

D2287R00103 Observational study of obstructive lung disease (NOVELTY)
A NOVEL observational longiTudinal studY on patients with a diagnosis or suspected diagnosis of asthma and/or COPD to describe patient characteristics, treatment patterns and the burden of illness over time and to identify phenotypes and endotypes associated with differential outcomes that may support future development of personalised treatment strategies

Year 5 Synopsis

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Table of Contents

1	BACKGROUND AND RATIONALE.....	1
2	OBJECTIVES.....	2
2.1	Primary Objectives.....	2
2.2	Secondary Objectives	2
2.3	Exploratory Objectives.....	3
3	METHODS.....	3
3.1	Inclusion Criteria and Exclusion Criteria	3
3.2	Variables Collected at Year 5	4
3.3	Statistical Methods	4
4	RESULTS.....	5
4.1	Patient Demographic and Clinical Characteristics	5
4.1.1	Patient Disposition, Demographic Characteristics, and Clinical Characteristics	5
4.1.2	Respiratory Disease Characteristics	5
4.1.3	Respiratory and Non-respiratory Comorbidities	5
4.1.4	Lung Function Data	6
4.1.5	Smoking History	6
4.1.6	Exposures During Childhood or Adult Life.....	6
4.1.7	Biomarkers	6
4.2	Medications.....	7
4.2.1	Airways Medication—Maintenance Therapy	7
4.2.2	Short-acting Beta-agonist Use and Reliever Medication	7
4.3	Exacerbations—Data from eCRF.....	7
4.4	Healthcare Resource Utilisation	8
4.4.1	HCU during Exacerbations—Data from eCRF.....	8
4.4.2	Respiratory-related and Non-respiratory-related Visits and Hospitalisations—Data from eCRF	8
4.5	PROs	9
4.6	Concordance between Diagnosis According to Guidelines and the Most Recent Clinician Diagnostic Label (Asthma and/or COPD)—Data from PRO and eCRF	9
4.7	Changes Between Baseline and Year 5	9
4.8	Differences between Physician-reported and Patient-reported Severity	9
4.9	Impact of COVID-19 Pandemic on Respiratory Disease Burden, Disease Progression, and Patient Behaviors	10
5	REFERENCES.....	11

1 Background and Rationale

Asthma and chronic obstructive pulmonary disease (COPD) are associated with substantial symptom burden, functional impairment, and mortality.^{1,2} Although they are often viewed as distinct disorders, both are now acknowledged as heterogeneous and overlapping obstructive lung diseases.^{3,4} Clear evidence exists that patients may have different lung function trajectories^{5,6} that are potentially influenced by genetic and clinical factors.⁷ Furthermore, exacerbation-prone populations have also been identified among individuals with asthma and COPD.^{8,9} Variations in environmental exposure, disease management, and access to care and medicines also contribute to the considerable disparities seen in asthma outcomes worldwide.¹⁰ To improve outcomes, a greater understanding of patient phenotypes (observable characteristics) and endotypes (distinct molecularly defined functional or pathobiological pathways that may be associated with distinct treatment responses)¹¹ is required across obstructive lung disease and over time. Biomarkers (defined characteristics measured as an indicator of normal biologic processes, pathogenic processes, or responses to an intervention¹²) are key to understanding phenotypes and distinguishing their underlying molecular endotypes, which may help define future therapeutic strategies for distinct patient subgroups.

Clinical trials exclude up to approximately 95% of patients with asthma or COPD seen in clinical practice,¹³ and the ecology of care can differ considerably from that in clinical practice.¹⁴ These factors can limit the generalisability of data on which clinical guidelines are largely based. Recent observational studies have provided valuable insights into patient characteristics and associated genetics, biomarkers, and phenotypes.^{4,15-20} However, those studies generally focused on asthma or COPD,^{21,22} were restricted to distinct geographies,^{23,24} or studied more severe or intensively monitored and treated disease. An increasing demand exists for longitudinal observational data on patients across the spectrum of obstructive lung disease, including those with comorbidities and from diverse clinical settings, to understand underlying mechanisms. Also, the COVID-19 pandemic significantly impacted the behaviour and management of patients with obstructive lung disease, and it remains unclear as to whether exposure to SARS-CoV-2 results in more severe manifestations in patients with asthma and/or COPD or whether treatment patterns have been adjusted by healthcare professionals in response to either COVID-19-related illness or perceived risk.

NOVELTY was a global, prospective, observational, 5-year study (including a maximum of up to 2 years of extension follow-up period for a subset of patients), which aimed to fill the abovementioned gaps in evidence by recruiting real-world patients, unlike clinical studies with restrictive inclusion/exclusion criteria. NOVELTY's primary objectives are to describe patient characteristics, treatment patterns, and disease burden over time, and to identify phenotypes and molecular endotypes associated with differential outcomes in patients with a diagnosis/suspected diagnosis of asthma and/or COPD. This synopsis describes objective, methods, results, and conclusion from analyses of data collected in Year 5.

2 Objectives

The following primary, secondary, and exploratory objectives were addressed for patients with a diagnosis or suspected diagnosis of asthma and/or COPD in the entire NOVELTY study. Where analyses are not included in this extension study report, they are flagged accordingly.

2.1 Primary Objectives

This study's primary objectives were to:

- To describe patient characteristics, treatment patterns and the burden of illness over time for individuals in clinical practice with a diagnosis, or suspected diagnosis, of asthma and/or COPD. Data will be described for the population overall and by pre-specified subgroups, including by demographics, exposures, symptom history, treatment history, concurrent clinical features, treatment setting, socioeconomic setting and access to healthcare

Note: for the Year 5 extension study, patient characteristics, treatment patterns and the burden of illness were segmented only by the most recent physician-assigned severity.

To identify phenotypes and endotypes, based on biomarkers and/or clinical parameters that are associated with differential outcomes for symptom burden, clinical evolution and healthcare resource utilisation, in individuals with a diagnosis, or suspected diagnosis, of asthma and/or COPD

2.2 Secondary Objectives

This study's secondary objectives were to:

- In patients with a diagnosis or suspected diagnosis of asthma and/or COPD, to compare their current diagnostic labels and physician-assessed disease severity with existing international criteria and phenotypic groupings
- To describe patient characteristics, symptom burden, quality of life, exacerbation rates, and clinical progression over time, by phenotype and endotype, for: (a) patients with recent-onset chronic respiratory disease, (b) patients considered by physician assessment or by specified criteria to have mild disease at enrolment, and (c) patients considered by physician assessment or by specified criteria to have severe disease at enrolment

Note: this objective was not included in the Year 5 extension study

- To describe the association between specified biomarkers, at enrolment and over time, and evaluate their stability over time, factors affecting their variability, and their relationships with clinical features, among patients with airways disease.

Note: this objective was not included in the Year 5 extension study

- To describe and compare the impact of the COVID-19 pandemic on respiratory disease burden, disease progression, and patient behaviors.

2.3 Exploratory Objectives

In patients with a diagnosis or suspected diagnosis of asthma and/or COPD, this study's exploratory objectives were to:

- To describe healthcare resource use overall and related to respiratory diseases
- To describe patient-reported outcomes (PROs), e.g. symptom assessment, health status, disease control, impact on daily activity and quality of life
- To assess the occurrence of exacerbations and other conditions, including upper and lower respiratory tract infections (RTIs) and SARS-CoV-2 infection, including seasonal variations, and their relationship with clinical outcomes

Note: this objective was not included in the Year 5 extension study

- To assess the adequacy of EMR in some countries for obtaining data about characteristics, clinical progress, and treatment of patients with obstructive airways disease.

Note: this objective was not included in the Year 5 extension study

- To assess the major criteria by which clinicians currently assign disease severity in patients with obstructive airways disease

Note: this objective was not included in the Year 5 extension study

- To assess the perception of their disease severity by patients.

3 Methods

NOVELTY was a global, prospective, observational, longitudinal study enrolling patients with asthma and/or COPD from primary and specialist clinical practices in 19 countries (ClinicalTrials.gov identifier: NCT02760329). All patients enrolled in the NOVELTY study were followed yearly for 3 years. Data collected at yearly intervals during this period include clinical assessments, spirometry, PROs, and healthcare utilisation (HCU). A subset of patients who participated in the NOVELTY main study period were enrolled into the extension period of the study and were followed up for a maximum total additional duration of 2 years post the planned main study period closure (Q2 2021). During this "Year 5" extension period, additional patient-reported data were collected via ad hoc patient questionnaires on an expected maximum of three separate contacts, and key clinical assessments were done at a single additional site visit. If data were not re-entered at Year 5, then the baseline, Year 1, Year 2, or Year 3 values (most recent available data) were used.

3.1 Inclusion Criteria and Exclusion Criteria

Patients who met all the following criteria were included in this study: 1) diagnosis or suspected diagnosis of asthma and/or COPD, according to physician judgment; 2) age ≥ 12 years; 3) willing and able to sign written informed consent (or having a responsible, legally authorised representative acting on patient's behalf who was willing and able to sign informed consent); and 4) enrolled through an active clinical practice.

Patients who met any of the following criteria were excluded from the study: 1) patients who participated in any respiratory interventional trial during the 12 months prior to enrolment or at enrolment; 2) patients who, in the opinion of their physician, were unlikely to complete three years of follow-up; and 3) patients whose primary respiratory diagnosis (i.e., the condition causing most of their respiratory symptoms) was not asthma or COPD—however, a co-diagnosis of another respiratory disease, such as bronchiectasis or interstitial lung disease with asthma or COPD, was accepted.

3.2 Variables Collected at Year 5

In addition to the variables collected at baseline, Year 1, Year 2, and Year 3, the following variables were collected at Year 5:

- Physiologic: height, weight, calculated body mass index (BMI), waist circumference, heart rate, pregnancy status
- Asthma/COPD information: patient diagnosis, disease severity, age at diagnosis, personal and family history of asthma/COPD and allergies, early critical lung health events (collected using ad hoc patient questionnaire), comorbidities, asthma/COPD complications, exacerbations, respiratory diseases, symptom assessments/disease control status (PRO), lung function measurements, and bronchodilator reversibility test
- COVID-19 assessments: COVID-19 infection, COVID-19 impact on patient behaviours and lifestyle (collected using ad hoc patient questionnaire), COVID-19 vaccine (reported as a concomitant medication), emergency room visits, hospitalisations, and procedures due to COVID-19 infection
- Risk factor assessments: smoking status and history, occupational exposure to pollutants, and allergens
- Impact on daily activity and health-related quality of life: health-related quality of life and patient-reported severity (collected using ad hoc patient questionnaire)
- Treatment(s) during previous 12 months: asthma/COPD treatments (treatment duration and posology)
- HCU during previous 12 months: medications, emergency and non-emergency physician visits, invasive and non-invasive ventilator use, hospitalisations and procedures, out-of-pocket expenses, emergency room visits, hospitalisations, and procedures due to exacerbations

3.3 Statistical Methods

For continuous variables, descriptive statistics included the number of patients (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients within the diagnostic label (column headers) unless otherwise indicated in the row label (i.e., will not necessarily sum to 100%). For therapy tables, the percentages were based on the number of patients with a maintenance or reliever therapy. Geometric means were calculated for all biomarker after changing zeros to 0.001. The proportions of patients missing data were reported each variable as applicable.

All summaries were presented for all patients for Year 5. Patients were stratified by their physician-assigned diagnostic label (asthma, COPD, asthma and COPD [or suspected]) for each of the specific analysis sets.

4 Results

4.1 Patient Demographic and Clinical Characteristics

4.1.1 Patient Disposition, Demographic Characteristics, and Clinical Characteristics

Overall 1,851 patients were included in the Year 5 analysis (990 [53.5%] with asthma, 469 [25.3%] with COPD, and 392 [21.2%] with asthma + COPD). Patients were, on average, 59.8 years old (SD: 13.5), 55.9% of the patients were female, and approximately three-quarters were Caucasian (75.6%).

More than one-third (36.7%) of patients were retired and 5.7% were not working due to poor health; less than half of patients (41.7%) had education beyond high school. Patients with asthma were younger, were more likely to be female, were less likely to be Caucasian, and were noticeably less likely to not work due to poor health than patients with COPD and patients with asthma + COPD.

The mean BMI of overall patients was 28.2 kg/m² (SD: 6.6) and mean waist circumference was 97.2 cm (SD: 17.2). Pregnancy status was reported for almost all (99.4%) women (0.8% [n=8] of women were pregnant).

4.1.2 Respiratory Disease Characteristics

The average age at onset of first respiratory symptoms consistent with physician diagnosis was 37.7 years (SD: 22.2); the average time since diagnosis was 16.2 years (SD: 15.1) for asthma and 6.0 years (SD: 5.6) for COPD. Almost all (82.8%) diagnoses reported in 5 years prior to study enrolment were based on symptom patterns. A little more than two-thirds of patients (68.3%) had no childhood respiratory symptoms. Only 4.7% of patients had pneumonia, which resolved, in the last 12 months prior to entry into the study. Patient disease severity levels were generally distributed evenly in the asthma and asthma + COPD groups (30.1% mild, 45.0% moderate, and 24.8% severe) and the COPD and asthma + COPD groups (25.9% mild, 44.6% moderate, and 29.5% severe). Patients with asthma were much younger at onset of first respiratory symptoms, and a lower proportion of patients with COPD had childhood respiratory symptoms compared with the other two groups.

4.1.3 Respiratory and Non-respiratory Comorbidities

Just 1.1% of patients had at least one respiratory comorbidity, with the most prevalent being obstructive sleep apnoea (0.3%). Only 8.7% of patients reported at least one non-respiratory comorbidity. The most prevalent non-respiratory comorbidities, across disease groups, was anxiety (3.0). The asthma + COPD group had a higher proportion of patients with ≥1 non-respiratory comorbidity than other groups.

4.1.4 Lung Function Data

Data on each lung function measure were available for more than 45% of patients. The average forced expiratory volume in one second (FEV₁) pre-bronchodilator measurement was 2.0 L (SD: 0.9) and 73.6% predicted (SD: 24.9) for all patients, and the average FEV₁ post-bronchodilator measurement was 2.1 L (SD: 0.9) and 78.6% predicted (SD: 25.2) for all patients. These measures were higher in patients with asthma.

4.1.5 Smoking History

About half of the patients (54.0%) were former smokers, 32.5% never smoked, and 13.5% were current smokers. The most common method was using cigarettes (61.9%). Average consumption duration reported by those patients with non-missing data was 33.8 pack-years (SD: 30.4). Patients with asthma were more likely to have never been smokers and consumed less tobacco than other patients.

4.1.6 Exposures During Childhood or Adult Life

Approximately three-quarters of patients (77.3%) had at least one parent who smoked during their childhood. The average duration of exposure to tobacco products in the household and/or workplace was 12.6 years (SD: 7.7) until the age of 18 and was 20.7 years (SD: 17.9) after the age of 18. Over half (58.4%) the patients had no exposure to dust or fumes at work, and 55.7% of patients had no exposure to any indoor allergens in the last month. Patients with asthma, compared with patients in other disease groups, had shorter durations of exposures to tobacco products in the household and/or workplace after the age of 18 and were less likely to be exposed to dust or fumes at work. Patients with COPD were less likely to have been exposed to any indoor allergens in the last month than patients in the other disease groups.

4.1.7 Biomarkers

Average values for the haematologic biomarkers were: (all units 10⁹/L unless otherwise noted)

- Haemoglobin: 138.0 g/dL (SD: 13.1)
- Haematocrit: 42.0% (SD: 3.9)
- Total leukocyte count: 7.3 (SD: 2.2)
- Lymphocytes: 1.8 (SD: 0.7)
- Eosinophils: 0.2 (SD: 0.2)
- Neutrophils: 4.7 (SD: 1.9)
- Basophils: 0.1 (SD: 0.0)
- Platelets: 270.4 (SD: 75.1)
- Monocytes: 0.5 (SD: 0.2)

Most patients (54.8%) had eosinophil values between 100–300 cells/uL.

4.2 Medications

4.2.1 Airways Medication—Maintenance Therapy

Inhaled corticosteroid (ICS): The average daily dose for ongoing ICS use at Year 5 was 998.1 budesonide (BUD) equivalent mcg per day (SD: 578.7). Daily dose categories (low/medium/high) were approximately evenly distributed across patients. Patients with COPD used a lower daily dose of ICS.

Chronic oral corticosteroid (OCS): The average daily dose of chronic (continuous) OCS use was 13.2 in Prednisolone equivalent mg (SD: 18.7).

Triple therapy: The combinations for three triple therapies used were ICS/long-acting β_2 agonist (LABA) + long-acting muscarinic antagonist (LAMA) (18.5%), ICS/LABA/LAMA (14.7%), and LAMA/LABA + ICS (2.2%). Overall, triple therapy was much less common among patients who used low-dose ICS than those who used medium- or high-dose ICS (23.8% for low, 39.0% for medium, 37.2% for high ICS dosage). Patients with asthma were noticeably less likely to have been using any triple therapy.

Biologics: The most used biologic was omalizumab (4.2%). Patients with asthma were more likely to use omalizumab than other patients; no patients with COPD used omalizumab, although small numbers of patients were involved.

LAMA and LABA: LAMA monotherapy was used by 26.6% of patients, LABA monotherapy by 2.1%, and combination treatment with LAMA/LABA or LAMA+LABA by 12.7%. Patients with asthma were less likely to use LAMA; patients with COPD were more likely to use LAMA/LABA or LAMA+LABA.

Add-on therapies: A total of 26.4% of patients used at least one of the add-on therapies (leukotriene receptor antagonists [LTRA], methylxanthine, macrolide, immunosuppressants). Patients with COPD were the least likely to have used add-on therapy.

By physician assessment: Patients classified as mild were less likely to have used maintenance therapy during Year 5, had used lower doses of ICS, and were less likely to used ongoing triple therapy. The above findings of treatment across diagnostic groups in the overall sample mostly hold by severity of condition.

4.2.2 Short-acting Beta-agonist Use and Reliever Medication

Less than half (44.8%) of patients indicated that they used short-acting beta agonist (SABA) inhalers as reliever medication, with an average use of 6.3 inhaler cannisters (SD: 13.1) during the past 12 months and 17.3% of patients using more than 12 inhaler cannisters during the past 12 months. The most frequently used reliever medication was salbutamol (54.4%). Patients with asthma were less likely to have used SABA inhalers.

4.3 Exacerbations—Data from eCRF

During the 12 months before the extension study visit, 28.4% of patients experienced at least one exacerbation. Patients who experienced at least one event experienced, on average, 1.8 (SD: 1.6) exacerbations during the 12 months before the extension study visit. Patients with asthma + COPD were

more likely to have experienced an exacerbation and experienced more exacerbations than other patients. Most of the exacerbation events lasted for no more than 1 month (27.6% for 1 week or less and 62.7% between 1 week and 1 month). The most common potential event preceding an asthma or COPD exacerbation was chest congestion (56.9%). Most of the symptoms (65.6%) were present for less than a week prior to an exacerbation. The majority (77.3%) of exacerbations were preceded by a cold or flu symptom cluster (including cold or flu, runny or stuffy nose, change in phlegm colour or stickiness, sore throat, shivers, chest congestion, and coughing up coloured mucus). Patients who experienced such exacerbations encountered these events, on average, 1.3 times (SD: 1.5) during the 12 months before the extension study visit. Patients with asthma + COPD were less likely to experience exacerbations of less than 1 week.

4.4 Healthcare Resource Utilisation

4.4.1 HCU during Exacerbations—Data from eCRF

At the patient-level basis, 20.0% of patients had at least one exacerbation treated with OCS, 0.9% had at least one exacerbation treated with injectable corticosteroids, and 18.0% with antibiotics. At the exacerbation event level, two-thirds of the exacerbation events were treated with OCS (72.1%), 2.6% were treated with injectable corticosteroids, and 63.5% were treated with antibiotics. In total, 4.6%, 11.3% and 3.5% of all patients experienced at least one accident and emergency (A&E) visit (not leading to hospitalisation), one unscheduled non-emergency visit to a clinic or hospital (not leading to hospitalisation), and hospitalisation for more than 24 hours due to exacerbation, respectively, and 14.9%, 35.4%, and 9.3% for reasons other than asthma or COPD, respectively. Patients with asthma + COPD were more likely to have their exacerbations treated with OCS or antibiotics than other patients. Exacerbations experienced by patients with asthma were noticeably less likely to be treated with antibiotics. Patients with asthma were less likely to have used A&E services and less likely to have been hospitalised for more than 24 hours due to exacerbation and were also less likely to have been hospitalised for more than 24 hours for any reason other than asthma or COPD.

4.4.2 Respiratory-related and Non-respiratory-related Visits and Hospitalisations—Data from eCRF

Among the 908 exacerbations with detailed information, 77 (8.5%) resulted in hospitalisations with lengths of stay ranging from one night (15.6% of hospitalisations) to eight nights or more (22.1% of hospitalisations); 5.2% of these hospitalisations included stays in the intensive care unit (ICU), with lengths of ICU stay ranging from one night (1.3% of hospitalisations) to eight or more nights (2.6% of hospitalisations).

Of all the patients, 14.9% had at least one A&E visit that did not lead to hospitalisation and 35.4% had at least one unscheduled non-emergency visit. A total of 9.3% had at least one hospital admission for more than 24 hours that were not related to respiratory reasons. Of patients with at least one hospital admission, 12.7% were re-admitted for the same reason within 30 days of being discharged. More than half (56.5%) of the patients who spent at least one night in the hospital (for any reason other than asthma or COPD) had a length of stay of at least four nights. Two patients (15.4% of patients who spent time

overnight in the ICU) were in the ICU for just one night (15.4%). Patients with asthma were less likely to have had at least one non-respiratory-related hospital admission for more than 24 hours.

4.5 PROs

The average Chronic Airways Assessment Test (CAAT) score for all patients completing the CAAT was 13.3 (SD: 8.5), with a lower mean for patients with asthma. The average Respiratory Symptoms Questionnaire (RSQ) total score for patients completing the RSQ was 4.3 (SD: 4.2), with a lower mean for patients with asthma. The average Modified Medical Research Council (mMRC) score for patients completing the mMRC was 1.2 (SD: 1.1), with a lower mean for patients with asthma. From St. George's Respiratory Questionnaire, 27.6% (n=345) of patients reported frequent productive cough, and patients with asthma were less likely to report frequent productive cough. The average EQ-5D-5L VAS score for patients completing the EQ-5D-5L VAS was 69.8 (SD: 19.8). Patients with asthma had a higher mean EQ-5D-5L VAS score.

4.6 Concordance between Diagnosis According to Guidelines and the Most Recent Clinician Diagnostic Label (Asthma and/or COPD)—Data from PRO and eCRF

The diagnostic symptoms of smoking history and respiratory measures were reported by physicians on the eCRF and the RSQ score was taken from the PRO.

Among all the patients who filled out the RSQ, 77.3% had respiratory symptoms. Among patients who reported being a current or former smoker at any time up to Year 5, 20.0% were current smokers and 80.0% were ex-smokers. Among patients who had post broncho dilator at Year 5, 52.0% had post-bronchodilator FEV₁/forced vital capacity (FVC) <0.7. Among patients who filled out the RSQ, reported being a current or former smoker, and had post broncho dilator at Year 5, 35.8% met one of these measures. Patients with a confirmed asthma diagnosis were noticeably less likely to have respiratory symptoms, be current smokers (more likely to be ex-smokers), and to have post-bronchodilator FEV₁/FVC <0.7.

4.7 Changes Between Baseline and Year 5

The physician-assigned diagnosis and severity of disease remained unchanged for most patients between baseline and Year 5. For all diagnoses, in patients classified as having mild disease at baseline, around 30% of patients progressed to moderate (26.5%) or severe (4.0%) disease in the Year 5 analysis set.

4.8 Differences between Physician-reported and Patient-reported Severity

Among all 1,851 patients, 61.8% of patients assessed as mild level of disease by a physician reported mild level, 46.0% of patients assessed as moderate level by a physician reported moderate level, and 40.9% of patients assessed as severe level by a physician reported severe level.

4.9 Impact of COVID-19 Pandemic on Respiratory Disease Burden, Disease Progression, and Patient Behaviors

Among all 1,615 patients who completed the questionnaire, 402 (24.9%) believed they had a COVID-19 infection, and 272 (16.8%) reported being told by a healthcare provider that they had COVID-19. Patients with asthma were more likely to report having COVID-19. A total of 43 (2.7%) had an emergency room visit, 28 (1.7%) had a hospitalization, and 10 (0.6%) were admitted to critical/intensive care because of COVID-19 infection. Most patients (95.0%) had received a COVID-19 vaccination. Nearly half (45.0%) strongly agreed they did not see friends and family because of the pandemic, and 24.1% strongly agreed their contacts with healthcare providers were impacted. Nearly one-third (32.3%) of patients neither agreed nor disagreed that they took regular medicines more strictly because of the pandemic. A total of 31.4%, 30.5%, and 32.1% of patients neither agreed nor disagreed that they took more time exercising, made effort to lose weight, and made lifestyle changes to improve health because of the pandemic, respectively, and 30.4% disagreed. Patients' attitudes on behavioral changes/adjustment because of the pandemic are generally the same among different diagnostic groups.

Early critical lung health events: A total of 345 (21.4%) patients had childhood breathing issues, and 287 (17.8%) patients had a childhood asthma diagnosis. One-tenth of the patients (10.2%) had a childhood hospital admission due to breathing problems, and 19.5% had limitation of physical activities due to breathing problems. Only 64 (4%) of the patients were delivered via caesarean section. Patients with COPD were less likely to have early critical lung health events than those with asthma or asthma + COPD.

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