Medicom International Conference Series in Pulmonology

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PEER-REVIEWED CONFERENCE REPORT

False-Negative SARS-CoV-2 PCRs: A Real Problem

Diagnosis of COVID-19 cannot be based solely on PCR test results, as a negative PCR does not rule out the presence of the virus, so include other tests like platelet counts and CRP.

read more on PAGE 3

Off-Season RSV Epidemics

Respiratory illnesses like respiratory syncytial virus (RSV) circulated at historically low levels during the COVID-19 pandemic, but spiked in several countries after relaxation of lockdown measures. What next?

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Air Pollution & Prenatal Lung Development

Significant negative associations during the second trimester of pregnancy were found between air pollution and postnatal lung function. Preterm infants showed higher susceptibility to air pollution exposure.

read more on PAGE 16

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Editor Prof. Richard Dekhuijzen, Radboud University Medical Center, the Netherlands

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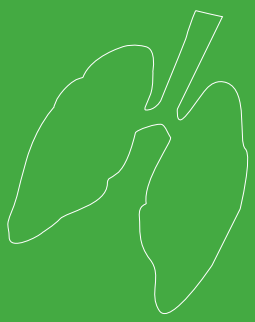

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Letter from the Editor

Prof. Richard Dekhuijzen

Dear colleagues,

As expected, the ERS of 2021 was held online, due to the COVID-19 pandemic. Again, numerous speakers were able to present the most recent updates in important areas of pulmonary diseases. Some of these studies and findings are highlighted below.

Interpretation of a negative SARS-CoV-2 PCR test can be difficult due to its lower sensitivity. COVID-19-suspected patients with increased inflammation markers were at increased risk of a first false-negative PCR test. The diagnosis should therefore not only rely on PCR test results, but also on inflammatory markers, such as platelet counts and CRP, clinical presentation, and findings from other tests, such as a chest CT scan.

Months after infection with SARS-CoV-2, some patients are still suffering from fatigue. In a recent study, severe fatigue negatively correlated with disease severity. Even patients with mild symptoms showed fatigue up to 10 months after initial infection.

Contrary to the current believe that only the elderly are at high risk for COVID-19, significant morbidity was seen in younger patients. While heart disease could be considered as a baseline risk factor, hypoxemia, LDH, and lymphocyte count were predictors of poor evolution. In contrast, anosmia and chest pain were associated with a better prognosis.

Infants of mothers who are exposed to higher air pollution during pregnancy may have reduced lung function development. Significant negative associations during the second trimester of pregnancy were found between air pollution and postnatal lung function. Preterm infants showed significant higher susceptibility to air pollution exposure, leading to impaired postnatal lung function.

Biomarkers are key to understanding asthma phenotypes and may help in distinguishing patient subgroups to guide therapeutic strategies. In the NOVELTY study, markers such as blood eosinophils, fractional exhaled nitric oxide (FeNO), and atopy history did not distinguish severe asthma from severe uncontrolled asthma.

This report outlines the most significant advancements discussed at the ERS conference. So, we hope that you will enjoy reading this Conference Report!

Stay healthy and kind regards,
Prof. Richard Dekhuijzen

Biography

Prof. P.N. Richard Dekhuijzen is Professor of Pulmonology at the Radboud University Medical Center in Nijmegen, the Netherlands. His specific area of clinical and research interest includes asthma, COPD, and inhalation technology. He studied medicine at VU Amsterdam and completed his training in pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam and in the Academic Hospital Nijmegen. In 1989, he finished his PhD thesis on training of the respiratory muscles in COPD, followed by a PhD thesis on steroid induced myopathy of the diaphragm in 1994 at the Catholic University Leuven (Belgium). He is author/co-author of over 330 peer-reviewed papers and many textbook chapters on respiratory medicine. From 2008-2010, he was Head of the Cardiology Department at Radboudumc. Until 2016, he chaired the Department of Pulmonary Diseases, the Heart-Lung Centre Nijmegen, and the Medical Staff at Radboudumc. He is the scientific chair of the Aerosol Drug Management Improvement Team (ADMIT) and chair of the Dutch Inhalation Technology Working Group. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Conflict of Interest Statement:
In the last 3 years, Richard Dekhuijzen and/or his department received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sandoz, Teva, and Zambon.

Listen to the Interview with Prof. Richard Dekhuijzen

LISTEN TO THE INTERVIEW

COVID-19 Research: Looking Back and Moving Forward

Higher inflammation markers in COVID-19 patients with a first negative PCR test

Interpretation of a negative SARS-CoV-2 PCR test can be difficult due to its lower sensitivity. COVID-19-suspected patients with increased inflammation markers were at increased risk of a first false-negative PCR test. The diagnosis should therefore not only rely on PCR test results, but also on clinical presentation, inflammatory markers, such as platelet counts and CRP, or other tests, like a chest CT scan.

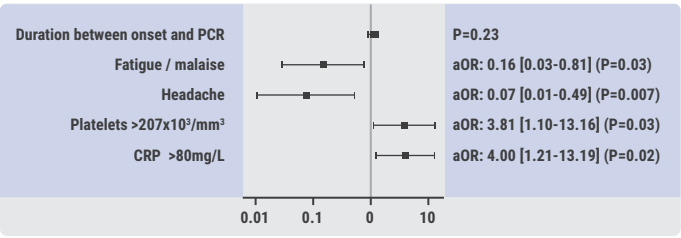
A rapid and accurate diagnosis of COVID-19 is essential, but symptoms are numerous and non-specific. Recently, concerns have been raised about the performance and real-life sensitivity of SARS-CoV-2 PCR testing. The interpretation of a negative PCR test can be difficult, as a negative result does not rule out the presence of the virus. Therefore, Dr Thomas Gille (Université Paris 13, France) and colleagues aimed to determine the clinical, biological, and radiological characteristics of patients with a false-negative first PCR test, but a final diagnosis of COVID-19 [1,2]. A secondary aim was to assess the outcome of these COVID-19 patients with a first negative PCR.

This retrospective, multicentre, case-control study was conducted in patients admitted to 11 hospitals in France and Belgium. Patients were included between 30 March 2020 and 22 June 2020. Adult patients were included when hospitalised for COVID-19. Exclusion criteria were pneumonia with another causative agent, pregnancy, recent delivery, lactation, and guardianship.

In total, 138 patients were included in France, and 22 in Belgium. Of these patients, 80 PCR-negative cases were matched to 80 controls with a positive first PCR on age, sex, and initial admission unit (wards vs intensive care unit). Data was collected on demographics, symptoms, lab tests, thoracic CT scan findings, treatments, need and duration of mechanical ventilation, and outcome of discharge. Multiple logistic regression was used to analyse the data.

The final diagnosis of COVID-19 (n=80) was based on a thoracic CT scan in most patients (n=71, 89%), followed by a contagion history (n=15, 19%), subsequent positive PCR tests (n=11, 14%), and serological testing (n=2, 3%). Demographics and baseline characteristics did not differ between cases and controls. PCR tests were done after a median of 6 days in cases and 5 days in controls (P=0.27). Mortality, hospital length-of-stay, need for antiviral medication, and mechanical ventilation did not differ between the groups. Patients with platelet counts >207x10^3/mm^3 and/or CRP levels >79.8 mg/L were at increased risk of having a false-negative first PCR test (aOR 3.81, P=0.034; aOR 4.00, P=0.023, respectively; see Figure). Moreover, patients with non-specific symptoms as fatigue or headache had a lower risk of false-negative first PCR. The time between symptom onset and PCR test was not associated with test positivity.

Figure: Predictive factors of false-negative PCR [1]



In conclusion, patients with higher inflammation markers were at increased risk of false-negative first PCR. Patients with suspected COVID-19 but a negative first PCR test should be repeatedly tested by PCR. Alternatively, a CT scan should be used for diagnosis.

1. Gille T, et al. Predictors of negative first SARS-CoV-2 PCR despite final diagnosis of COVID-19 and association with outcome. Abstract 2662, ERS 2021, 5–8 September.
2. Lascarrou JB, et al. Sci Rep 2021;11(1):1–7.

Breathing techniques contributed to COVID-19 recovery

COVID-19 patients often deal with breathlessness, anxiety, and fatigue persisting months after the acute infection. Online programmes for teaching breathing techniques are feasible. Two home-based rehabilitation tools that

contributed significantly to recovery were presented in 2 studies. Both inspiratory muscle training (IMT) and opera singing helped to reduce dyspnoea in rehabilitation after COVID-19.

The recovery of COVID-19 is associated with prolonged symptoms, including breathlessness. Some patients even report breathlessness for more than 1 year after the acute infection so there is an urgent need for identifying rehabilitation strategies. Prof. Melitta McNarry (Swansea University, UK) and colleagues therefore investigated the role of IMT in COVID-19 recovery [1]. In addition, The English National Opera (ENO) conducted an online programme, which is not a singing group, but an intervention that uses singing techniques to aid recovery from COVID-19 [2].

In the IMT programme, adults recovering from self-reported COVID-19 were included in the study. Shortness of breath was the primary inclusion criteria. A total of 250 participants (median age 48 years) were randomised 4:1 to the IMT programme or the control group. The intervention group followed IMT sessions 3 times per week for an 8-week period at 80% maximal capacity. The sessions took place remotely through Zoom. At baseline and post-intervention, breathlessness (King's Brief Interstitial Lung Disease [KBILD] Questionnaire), respiratory muscle strength, fitness (Chester Step Test), and physical activity were assessed.

Results showed that IMT improved all domains of the KBILD; dyspnoea was significantly reduced by 33% (P<0.001). Significant improvements were also obtained in maximal inspiratory pressure, fatigue index, and fitness (all P<0.001). However, no improvement on physical activity nor on sleep was observed.

For the ENO programme, the ENO and an NHS trust collaborated to create ENO Breath: a 6-week online programme teaching breathing techniques and lullabies to COVID-19 patients. A pilot of ENO Breath was run for people with persistent dyspnoea at outpatient follow-up, >8 weeks after hospital discharge. Patients with persistent dyspnoea post-acute illness were encouraged by clinical staff to self-refer to ENO Breath, provided they met the following medical criteria: normal chest radiology, normal resting and exertional SpO_2, normal basic blood tests, and optimised pre-existing respiratory or cardiology comorbidities. Patients completed pre- and post-programme questionnaires about dyspnoea (visual analogue scale 0–10), anxiety (GAD7), and wellbeing (RAND36). Participants' views were discussed in focus groups and post-programme written surveys.

During ENO Breath pilot, 135 participants with a mean age of 47 years completed the programme. Of these, 17 (13%) had been hospitalised due to COVID-19. Online attendance was high with participants attending an average of 5.5 out of 6 sessions (91%). After following ENO Breath, 112 (83%) participants reported improved dyspnoea over the 6 weeks. Moreover, a significant improvement in anxiety was observed: GAD7 went from 6 to 4 (P<0.001). Additionally, an improvement in social functioning (11%), energy and fatigue (8%), and physical functioning (8%) was seen. Patients described their experience as enjoyable, calming, and a useful distraction from their breathing. The breathing techniques helped participants to better cope with their daily symptoms. In addition, group sessions combatted loneliness and allowed for patients to connect with people in similar situations.

Both IMT and opera singing contributed to recovery following COVID-19. Only a limited number of sessions per week showed a clear improvement on symptoms as breathlessness, anxiety, and fatigue. Overall, both tools are acceptable and feasible for re-habilitation and should be considered for wider implementation.

1. McNarry M, et al. Late Breaking Abstract - A randomised control trial using inspiratory muscle training in post-COVID-19 rehabilitation. Abstract 169. ERS 2021, 5–8 September.
2. Owles H, et al. ENO breathe: An arts and health alliance to help COVID-19 recovery. Abstract 457. ERS 2021, 5–8 September.

Persistent fatigue following COVID-19

Months after infection with SARS-CoV-2, some patients are still suffering from fatigue. In the current study, severe fatigue negatively correlated with disease severity. Even patients with mild symptoms showed fatigue up to 10 months after initial infection.

Since the emergence of COVID-19, millions of people have been infected globally. Although cases of long COVID-19 are still increasing, little is known about long-term consequences of COVID-19. "One point that has become increasingly clear is that fatigue is the most reported symptom during recovery," Ms Zjala Ebadi (Radboud University Medical Center, the Netherlands) pointed out [1].

Ms Ebadi presented a study that aimed to determine the long-term prevalence of severe fatigue in patients after recovering from COVID-19 infection. Patients were recruited during their visit to the multidisciplinary aftercare facility; 3 study groups were distinguished: intensive care unit (ICU) patients, hospitalised non-ICU patients, and non-hospitalised patients referred by general practitioners (GP) for persisting

symptoms. Between May 2020 and May 2021, participants were examined during 2 consultations with a 2-month interval. Fatigue was assessed using Checklist Individual Strength in which severe fatigue was defined as a score ≥35.

In total, 236 patients were included in the study. Severe fatigue was present in 58% of ICU (n=31), 66% of hospitalised non-ICU (n=77), and 94% of GP-referred (n=128) patients during the first consultation (average 3.7 months after COVID-19), and in 52%, 64%, and 75% of patients during the second consultation (average 8.2 months after COVID-19).

In short, severe fatigue remained highly prevalent in both hospitalised and non-hospitalised patients, even up to 10 months after COVID-19. Future studies should focus on preventing COVID-19 fatigue to become chronic.

1. Ebadi Z, et al. Late Breaking Abstract - Post-Covid-19 fatigue and its associations with health status: long-term follow-up. Abstract 93. ERS 2021, 5–8 September.

Risk of COVID-19-related morbidity and mortality in young and middle-aged adults

Contrary to the current believe that only the elderly are at high risk for COVID-19, significant morbidity was seen in younger patients. While heart disease could be considered as a baseline risk factor, hypoxemia, LDH, and lymphocyte count were predictors of poor evolution. In contrast, anosmia and chest pain were associated with a better prognosis.

At the start of the COVID-19 pandemic it was generally thought that the disease was mostly affecting older adults, and that young people were more likely to have milder cases. However, at the moment, young and middle-aged adults are the largest group of COVID-19 patients. Dr Eva Tabernero Huguet (Hospital Universitario Cruces, Spain) explained that it is possible for the young to develop severe disease [1,2]. Therefore, Dr Tabernero Huguet and colleagues investigated clinical aspects in adults hospitalised for COVID-19, and identified risk factors for poor evolution.

In a multicentre, prospective study, 513 hospitalised COVID-19 patients with pneumonia aged 18–65 years were included from March 2020 to May 2020. The primary outcome was a composite of poor evolution: admission to intensive care unit (ICU) and/or use of non-invasive ventilation, new use of continuous positive airway pressure (CPAP), high flow nasal cannula oxygen, and death.

Of the included patients, 102 (19.8%) had poor evolution. The mortality rate was 3.9% (n=20), indicating that COVID-19 has significant morbidity in young and middle-aged adults. In addition, heart disease showed to be a risk factor (OR 5.41, 95% CI 1.72–16.60, P=0.003), while anosmia and chest pain had protective effects (OR 0.34, 95% CI 0.13–0.76, P=0.014; OR 0.19, 95% CI 0.03–0.74, P=0.033, respectively). Hypoxemia, LDH, and lymphocyte count were predictors of poor evolution (OR 0.72, 95% CI 0.65–0.80, P<0.001; OR 1.04, 95% CI 1.01–1.07, P=0.006; OR 0.46, 95% CI 0.24–0.87, P=0.017, respectively).

In conclusion, COVID-19 has a significant morbidity in younger and middle-aged patients with heart disease as the most important risk factor. Anosmia and chest pain showed to be protective.

1. Taberno Huguet E, et al. COVID-19 in young and middle aged adults. Predictors of poor evolution and clinical difference. Abstract 88. ERS 2021, 5–8 September.
2. Taberno Huguet E, et al. Infection 2021:1–11.

Fear of COVID-19 related to dyspnoea in COPD patients

People with long-term respiratory conditions like COPD are particularly impacted by COVID-19-related concerns. Stress and COPD frequently go together, and stress can lead to worsening of COPD symptoms. The current study proved a relationship between fear of COVID-19, stress, and dyspnoea.

The COVID-19 pandemic is having psychological impacts on people globally, with increased levels of stress and anxiety being reported, especially in people with pre-existing medical conditions who appear to be extra vulnerable. Stress may cause serious health problems as it weakens the immune system, and is therefore a known COPD trigger. Accordingly, the aim of the presented study was to investigate the relationship between the fear of COVID-19 and perceived stress and the dyspnoea in patients with COPD [1].

In this prospective study, participants received an online survey by email. The survey included demographic and clinical questions. The modified Borg scale (mBORG) was used to assess dyspnoea, the Fear of COVID-19 scale to assess fear of COVID-19, and the Perceived Stress Scale-10 (PSS-10) to assess stress.

A total of 33 patients with COPD were included; mean age was 60.1 years and 36% were female. Mean PSS-10 and

mBORG scores were 21.2 and 5.8, respectively. Strong positive correlations were found between the fear of COVID-19 and PSS-10 score (r=0.80; P<0.001) and mBORG score (r=0.70; P<0.001).

A significant relationship between fear of COVID-19 and stress and dyspnoea was found in COPD patients. Future studies should further investigate the negative consequences of stress in COPD patients with fear of COVID-19.

1. Aktan R, et al. The relationships between the fear of COVID-19 and perceived stress and dyspnea during the COVID-19 pandemic in patients with COPD: Preliminary findings of a prospective study. Abstract 341. ERS 2021, 5–8 September.

Respiratory Viral Infections: Insights from Recent Studies

Impact of COVID-19 on the dynamics of respiratory viruses

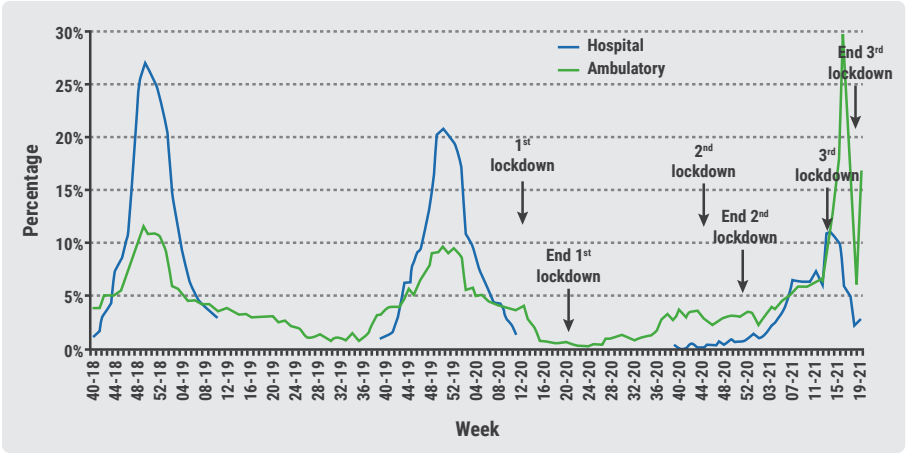
The impact of the COVID-19 pandemic and its associated lockdown on the circulation of other respiratory viruses is enormous. The natural course of seasonal viral infections has been deeply modified. A delayed or even non-existing respiratory syncytial virus (RSV), influenza, and rhinovirus season were seen in e.g. France, the UK, Italy, and Switzerland. These off-season viral epidemics might be explained by the COVID-19 measures. Delayed RSV epidemics may be a burden to healthcare systems that are already strained because of COVID-19.

There has been a dramatic global reduction in cases of respiratory seasonal viruses during the COVID-19 pandemic. Non-medical measures, such as social distancing, appear to have had a big impact on the course of natural epidemics of other respiratory viruses, including RSV.

In the first presented study, Prof. Ralph Epaud (Paediatric Hospital Crétiel, France) and his team aimed to assess the course of RSV infection in France during the 2020–2021 season, and compared it with the 2 previous RSV seasons (2018–2019 and 2019–2020) [1,2]. French national data for bronchiolitis in children under 2 years of age from 3 networks was analysed, including data from emergency departments (ED), general practitioners (GPs), and hospital laboratories. The RSV-positive tests during these visits were compared to the RSV-positive tests of the previous 2 RSV seasons.

During the 2020–2021 season, the RSV epidemic started in February 2020, which is 12 weeks later compared with the previous seasons (see Figure). The highest number of bronchiolitis cases was reported during the end of March 2021, almost 10–12 weeks later than the previous seasonal peaks. In addition, the total number of cases was lower than in the previous seasons. The absence of a normal RSV epidemic is presumed to be a result of COVID-19 restrictions, including social distancing. This led to raised concerns regarding the burden of RSV in the already overheated healthcare system because of the COVID-19 pandemic. The

Figure: Percentage of hospital and ambulatory positive test for RSV all ages, Metropolitan France, week 40 of 2018 till week 19 of 2021 [2]



occurrence of a delayed RSV epidemic in France could be explained by school and daycare centres that remained open in the second lockdown. Another explanation could come from the fact that despite international travel restrictions, interstate borders remained open, allowing RSV diffusion from other countries.

A second study looked at the incidence of respiratory viruses in a rural district general hospital in Shrewsbury, UK, during the (supposed) peak influenza season [3]. Ms Taya Chapman and colleagues performed a retrospective analysis on all respiratory swab data of hospitalised patients during the third and fourth week of January 2021. Respiratory analysis was done for influenza, RSV, and SARS-CoV-2 simultaneously.

Remarkably, zero patients of the investigated cohort tested positive for influenza or RSV. Of 247 patients, 120 (47%) tested positive for SARS-CoV-2, of which 66 (55%) were male with a mean age of 73 years. Although the sample size was small, the UK cohort reflected the trend of influenza cases represented in the Southern Hemisphere during the peak influenza season [4]. It might be that regular hand washing and masks prevented the spread of other respiratory viruses. Moreover, competitive inhibition of influenza and RSV by SARS-CoV-2 is likely through its binding of sialic acid receptors on the host's cell surface normally used by influenza viruses to gain entry into cells. However, future studies are needed to study this *in vitro*.

In a third study, Dr Sergio Ghirardo (Bambino Gesù Children's Hospital, Italy) explored the effects of SARS-CoV-2 containment measures on bronchiolitis onset, hospitalisation, aetiology, and severity in comparison with the 2 previous years [5]. Dr Ghirardo and his team performed a retrospective study in infants ≤1 year that were hospitalised because of bronchiolitis between 1 September and 31 December 2018, 2019, and 2020. Viral diagnosis was confirmed by PCR test.

The bronchiolitis season onset did not occur significantly later in the year in 2020 (P=0.93). However, the frequency of hospitalisation differed significantly, with only 5 hospitalised patients in 2020 compared with 36 in 2019 and 2018 (reduction of 86.2%). The in-hospital length-of-stay in 2020 was shorter (2.6 days) compared with 4.8 days in 2019 and 4.6 days in 2018 (P=0.02). No patients were submitted to the intensive care unit (ICU) in 2020, while 4 (11%) patients were admitted to the ICU in 2019, and 1 (3%) in 2018. According to the aetiology, rhinovirus accounted for all cases in 2020; no RSV cases were identified. The epidemic respiratory virus season did not start at the end of December 2020 presumably because of COVID-19 measures. Shorter length-of-stay and less ICU admissions suggested less severe disease as a possible consequence of COID-19 measures. Another explanation could be that less severe disease was seen because of a lack of RSV.

In a fourth study, Dr Cristina Ardura-Garcia (Institute of Social and Preventive Medicine, Switzerland) studied the effect of the COVID-19 measures on respiratory symptoms in children previously followed by paediatric pulmonologists [6]. Parents from children of The Swiss Paediatric Airway Cohort, a prospective cohort in Switzerland including children aged 0–16 years, were asked to complete monthly questionnaires on respiratory symptoms and treatment for 1 year. Questionnaires were compared to pre-lockdown questionnaires.

Among 536 questionnaires including 253 children with a mean age of 9 years, 83 were completed during the pre-COVID winter, 91 during lockdown, 258 during the COVID winter, and 104 during spring 2021. Compared to the pre-COVID winter, questionnaires completed in lockdown and in the COVID-winter were less likely to report on respiratory infections (aOR 0.12), cough (aOR 0.31), dyspnoea (aOR 0.30), wheeze (aOR 0.15), treatment for respiratory problems (aOR 0.022), and asthma control-drug use (aOR 0.65). Preventive measures reduced respiratory infections and symptoms drastically in Switzerland during the COVID-19 pandemic compared to the previous period. No further reduction of respiratory infections was seen during school closures.

In conclusion, an absent or delayed annual seasonal epidemic of most respiratory viruses was reported, likely related to implementation of public health measures because of COVID-19. While continued detection of rhinovirus was noticed, influenza and RSV were absent during the 2020-2021 season with France as an exception experiencing a 3-month delayed RSV season. Usually in the Northern hemisphere, influenza and RSV are known to peak during winter months. However, restrictions of international travel, school closures, and stay-at-home orders may have influenced the spread of these viruses.

1. Epaud R, et al. Late Breaking Abstract - Impact of COVID-19 social distancing on viral infection in France: a delayed outbreak of RSV. Abstract 2849. ERS 2021, 5–8 September.
2. Delestrain C, et al. Pediatr Pulmonol. 2021 Sep 2.
3. Chapman T, et al. Another aspect of COVID pandemic: where has all the Flu gone? Abstract 3255. ERS 2021, 5–8 September.
4. Hills T, et al. Lancet. 2020 Nov 21;396(10263):1633–1634.
5. Ghirardo S, et al. Delayed bronchiolitis season's onset during COVID-19 pandemic. Abstract 2963. ERS 2021, 5–8 September.
6. Ardura-Garcia C, et al. Effect of COVID19 preventive measures on respiratory infections and symptoms in children. Abstract 2962. ERS 2021, 5–8 September.

Cost-effectiveness of extending palivizumab duration

Infants at high risk of respiratory syncytial virus (RSV) usually only receive palivizumab during the first year of life. While children remain at risk of serious complications from RSV the subsequent year, the costs of passive vaccination with this monoclonal antibody would exceed the costs of RSV-related hospital admission.

Palivizumab, a monoclonal antibody against RSV, is an effective prophylaxis of RSV infection in high-risk infants. It is given once per month intramuscularly during the RSV season. When patients are no longer considered to be at increased risk, for example after the first year of life, they no longer qualify for the vaccination although they are still at risk of getting RSV.

In a retrospective cohort study, investigators evaluated the number of vaccinated children that were admitted to the hospital with RSV during the subsequent winter, to determine whether former high-risk paediatric patients developed significant RSV infection during subsequent years. They then compared the cost of palivizumab with length of hospital stay [1]. Electronic medical records of patients were screened to identify unvaccinated children from October 2016 to March 2018. Qualifying patients from the winters of 2016–2017 and 2017–2018 were compared against the following years.

Over the course of 2 winters, 22 patients were identified as having received palivizumab one year, but not qualifying for the subsequent year. Of these, 4 (18%) were admitted to the hospital with RSV the second year with a median stay of 6.5 days. All patients required non-invasive ventilation. The median payment required for each stay was £1,670 while the median costs of palivizumab treatment for these patients would have been £3,748 per patient.

So, while children remain at high risk of RSV despite no longer qualifying for palivizumab, results showed that costs of palivizumab exceeded that of hospital admission. Although the study is limited by its sample size, it seems that it is not cost-effective to extend the vaccination period.

1. Wilson G, et al. Palivizumab: Is it cost effective to extend the vaccination period for patients at risk of severe respiratory syncytial virus infection? Abstract 2845. ERS 2021, 5–8 September.

Rhinovirus bronchiolitis increased risk of recurrent wheezing and asthma

Respiratory syncytial virus (RSV)-induced bronchiolitis is a known risk factor for recurrent wheeze and asthma development. The presented systematic review and meta-analysis showed that infants with rhinovirus (RV)-induced bronchiolitis had an even higher risk for school age asthma compared with RSV.

Previous literature shows that 1 in 3 infants develop recurrent wheeze or asthma after bronchiolitis [1]. Respiratory viruses are the primary cause of bronchiolitis in infants. While there appears to be a causal relationship between RSV or RV infection and asthma development, research has only compared outcomes of RSV and RV bronchiolitis. This is the first systematic review to directly compare the associations of RSV and RV bronchiolitis with preschool wheeze and asthma development.

To this end, 4 databases were searched for articles using a MeSH term-based algorithm. After screening, 48 studies were included in the meta-analysis which was limited to cohort studies and randomised controlled trials. Outcomes of interest were recurrent wheeze and diagnosis of asthma.

Results showed that children with RV bronchiolitis were more likely to develop asthma than children with RSV (OR 2.49; 95% CI 1.41–4.40). In addition, the RV bronchiolitis group was more likely to develop recurrent wheeze than the control group (OR 4.55; 95% CI 2.01–10.29).

According to Dr Heidi Makrinioti (Imperial College London, UK), in this first meta-analysis comparing RSV- and RV-induced bronchiolitis as a risk factor for recurrent wheeze and asthma, recurrent wheeze and asthma were more likely to occur after RV bronchiolitis than after RSV bronchiolitis. Thus, future studies should focus on infants with RV bronchiolitis as a risk group.

1. Makrinioti, H. et al. The role of respiratory syncytial virus and rhinovirus in early recurrent wheeze and asthma inception – a systematic review. Abstract 2572. ERS 2021, 5–8 September.

No prognostic value of clinical scores for RSV mortality in stem cell transplant recipients

Respiratory syncytial virus (RSV) is one of the most commonly encountered respiratory viruses among patients who have undergone a stem cell transplant. Two clinical scores predicting the risk of progression to lower respiratory tract infection (LRTI) and death failed to show a prognostic value in this patient group.

Allogeneic haematopoietic stem cell transplant (HSCT) recipients are at increased risk of severe RSV infection, so identifying patients at risk can be helpful in guiding treatment. Until new treatments are being approved, ribavirin is the only

currently available treatment option. Two clinical scores were previously considered to predict the risk of progression to LRTI and death: the Immunodeficiency Scoring Index (ISI) from 2014 and the Severe Immuno-Deficiency (SID) score from 2008 (see Table) [1,2]. Current guidelines recommend to use ISI or SID scores to advise for treatment of RSV infection.

Table: Prognostic scoring systems: ISI and SID scores [1,2]

SID score (range 0–7)		ISI score (range 0–12)	
Low risk, MID: 0		Low risk: 0–2	
Moderate risk, SID: 1		Moderate risk: 3–6	
High risk, very SID: 2–7		High risk: 7–12	
ANC ≤0.4x10^9/L	1	ANC <0.5x10^9/L	3
ALC ≤0.1x10^9/L	1	ALC <0.2x10^9/L	3
Allogeneic HSCT <6 months ago	1	Allogeneic HSCT <1 month ago or pre-engraftment	1

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; ISI, immunodeficiency scoring index; MID, moderate immune-deficiency; SID, severe immune-deficiency

The aim of the current study was to assess the prognostic value of the ISI and SID score using a retrospective multicentre cohort of allogeneic HSCT recipients [3,4]. Both adult and paediatric allogeneic HSCT recipients diagnosed with an RSV infection between 2010–2019 were included in 5 hospitals in France. Patients were stratified into 3 risk groups according to their (retrospective) ISI or SID score. Endpoints were overall survival (OS), RSV-attributable mortality, and progression from upper respiratory tract infection (URTI) to LRTI.

Of 147 patients that were electable for the study, 94 (64%) were initially diagnosed with URTI and 53 (36%) with LRTI. At day 90, 14 patients died with an estimated survival rate of 91%. Cumulative incidence of LRTI after URTI at day 60 was 14%. The stratification of disease severity according to either ISI or SID score did not demonstrate any difference in either overall mortality or RSV-attributable mortality. However, the ISI score could predict the risk for progression from URTI to LRTI (P=0.0008).

In short, data from this multicentre retrospective study of allogeneic HSCT recipients with PCR-confirmed RSV infection showed that neither the ISI nor the SID score demonstrated prognostic value for mortality, but the ISI score allowed for the prediction of progression to LRTI. More research is needed for future implementation of the scores.

1. Khanna N, et al. Clin Infect Dis. 2008 Feb 1;46(3):402-12.
2. Shah DP, et al. Blood. 2014;123(21):3263–8.
3. Houist A, et al. Evaluation of two prognostic scoring systems for respiratory syncytial virus infection in a French multicentre cohort of allogeneic hematopoietic stem cell transplant recipients. Abstract 1893. ERS 2021, 5–8 September.
4. Houist A, et al. Bone Marrow Transplant. 2021 Sep 21;1-10.

COPD: Evidence Update

Livestock farming affected the airway microbiome of COPD patients

Intensive livestock production has been associated with health risks. Exposure to livestock farm emissions may lead to poor outcomes. The current study showed that residential exposure to livestock-emitted endotoxin was linked to increased species richness in COPD patients.

Living in a livestock-dense area has been associated with adverse health effects. Especially COPD patients may suffer from complications when living close to livestock. Livestock farm emissions involve excretion of gases, like endotoxin, which could be harmful to health. Mr Warner van Kersen (Utrecht University, the Netherlands) investigated whether livestock affects the airway microbiome of COPD patients [1]. In his study, the airway microbiome of COPD patients was compared with the microbiome of healthy controls.

Oropharyngeal swabs were taken from 283 participants (99 cases, 184 controls) in a livestock-dense area in the Southeast of the Netherlands at baseline, week 6, and week 12. Participants were non- or former smokers, and had not used antibiotics in the month prior to sampling. Cases differed from controls in age (P<0.001), years of smoking (P=0.001), use of lung medication (P<0.001), and use of antibiotics (P<0.002). Accordingly, oropharyngeal microbiota samples were analysed using 16S rRNA sequencing and the DADA2 pipeline.

Most samples were dominated by the bacteria *Streptococcaceae* and *Veillonellaceae*. No difference in species richness was observed for cases versus controls. However, an increased species richness was seen for atopy (β=7.02; 95% CI 1.25–12.78), medium versus low education level (β=6.67; 95% CI 0.001–13.33), and livestock-emitted endotoxin exposure (β=20.07;

95% CI 1.57–38.56). When data was stratified for cases versus controls, effects were only present in the cases group (see Table). No effect was seen of case-control status on microbiome composition, although a small gender effect was observed.

Table: Observed richness in cases and controls [1]

	Observed richness cases & controls		Observed richness			
			Controls		Cases	
Variable	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
COPD (case vs control)	-2.24	- 8.09–3.61	NA	NA	NA	NA
Gender (female vs male)	-0.17	- 5.49–5.16	-0.73	-7.54–6.08	2.65	-6.63–11.83
Atopy (yes vs no)	**7.02**	**1.25–12.78**	6.04	-1.31–13.38	**12.1**	**2.35–21.86**
Smoking history (former vs never)	-0.19	- 5.66–5.28	-2.8	-9.5–3.9	4.98	-5.07–15.04
Educational level (medium vs low)	**6.67**	**0.01–13.33**	4.17	-4.44–12.78	**13.65**	**2.52–24.78**
Educational level (high vs low)	1.29	-5.99–8.57	-1.25	-10.51–8.02	9.38	-3.36–22.12
Livestock emitted endotoxin (EU/m³)	**20.07**	**1.57–38.56**	8.44	-15.73–32.61	**42.73**	**12.88–72.59**
Season (spring vs winter)	0.02	-7.93–7.06	- 3.27	-12.17–5.63	6.48	-5.65–18.61
Season (summer vs winter)	4	-3.05–11.06	2	-6.17–10.72	6.88	-6.02–19.78
Season (fall vs winter)	-8.04	-18.04–1.96	-12.43	-28.41–3.56	-5.3	-18.59–7.98
Antibiotics within 4 weeks prior to sampling (yes vs no)	-3.39	-14.14–7.36	-12.17	-32.14–7.8	-0.53	-13.46–12.39

Abbreviations: NA, not applicable. Significant variables in bold.

To investigate the stability of the oropharyngeal microbiome over time, 20 randomly selected participants were evaluated over the course of 3 timepoints. Individual patterns over time could be distinguished, indicating stable differences between individuals.

In conclusion, an increase in species richness in COPD patients was associated with residential exposure to livestock-emitted endotoxin. Oropharyngeal microbiota in COPD patients and controls were relatively stable over a 12-week period, indicating that a single sample is representative for the individual oropharyngeal microbiota in COPD cases and healthy controls. Future analysis should include a multivariable analysis to evaluate independent drivers.

1. Van Kersen W, et al. The oropharyngeal microbiome of COPD patients and controls in a livestock dense area. Abstract 99. ERS 2021, 5–8 September.

Adherence to singing training similar to standard physical therapy in COPD patients

A randomised controlled trial found an equal adherence in COPD patients receiving singing training compared to physical training, making vocal training an attractive form of rehabilitation.

Pulmonary rehabilitation is essential to COPD care. However, maintaining high adherence rates can be challenging. In a previous multicentre, randomised controlled trial 'Sing-a-Lung', the authors already demonstrated that singing training was as effective as standard physical therapy in terms of change in 6-minute walking test (6MWT) and St George's Respiratory Questionnaire (SGRQ). The current analysis focused on the impact of adherence on these parameters [1].

The non-inferiority randomised controlled trial (NCT03280355) included subjects who had a prescription for pulmonary rehabilitation from August 2017 to August 2019. Participants were randomised to receive singing training or physical training. The primary outcome was a change in 6MWT from baseline to follow-up 2 weeks post-pulmonary rehabilitation. In a post hoc analysis, multivariable logistic regression analyses were performed on the relationship between adherence and achieving clinically significant improvement of 6MWT (30 metres) and SGRQ score (4 units) from baseline to post-pulmonary rehabilitation.

A total of 270 participants were included in the analysis, of which 195 (72%) completed the study. Proportions of patients with high adherence were similar between groups: 61% for singing and 57% for physical training (P=0.90). Medium adherence and high adherence were associated with higher odds of improving 6MWT (medium: OR 5.6; 95% CI 1.4–22.4; P=0.02 vs high: OR 10.5; 95% 3.0–36.6; P=0.001) and SGRQ (medium: OR 8.3; 95% CI 2.1–32.7; P=0.003 vs high: OR 17.0; 95% CI 4.9–58.3; P<0.001).

A positive dose-response relationship between adherence and improvements of 6MWT and SGRQ scores was found. In addition, equal adherence to singing versus physical training was observed. Although singing training sounds promising for COPD rehabilitation, there is still a way to go before the optimal content of vocal training is researched and standardised.

1. Kaasgaard M, et al. Adherence to singing training vs. physical training in COPD rehabilitation. Abstract 320. ERS 2021, 5–8 September.

COPD symptoms and lung function related to sleep quality

Patients with COPD are particularly vulnerable to poor sleep. The presented study showed that COPD symptoms and lung function were related to sleep quality. Diagnostics and treatment of sleep problems should be prioritised to improve life quality of these patients.

Sleep quality is often poor in patients with COPD. However, these night-time symptoms are frequently unnoticed. The goal

of the current study was to investigate the relationship between sleep quality, symptoms, and lung function in COPD patients [1]. A descriptive, analytic study with a cross-sectional design was conducted in COPD patients in the Harum Melati Clinic (Indonesia). Spirometry was performed to measure lung function, modified British Medical Research Council (mMRC) questionnaires were used to report symptoms, and sleep quality was quantified using the Pittsburgh Sleep Quality Index (PSQI) scale and stratified into good (PSQI score <5) and poor sleep quality (PSQI score >5). Spearman correlation was used to measure the strength of the correlation between variables.

The study included 203 subjects; most patients were male, and medium age was 62.4 years. Of investigated patients, 114 (71%) had good sleep quality and 59 (29%) had poor sleep quality. A moderate positive correlation was found between sleep quality and COPD symptoms (ρ=0.437; P=0.001), while a strong positive correlation was found between sleep quality and lung function (ρ=0.879; P=0.001).

Taken together, sleep quality in COPD patients correlated to symptoms and lung function. More research on diagnosis and treatment of sleep problems in COPD patients should be done to manage daily life of these patients.

1. Soemarwoto RA, et al. The correlation of sleep quality on symptoms and lung function in COPD. Abstract 940. ERS 2021, 5–8 September.

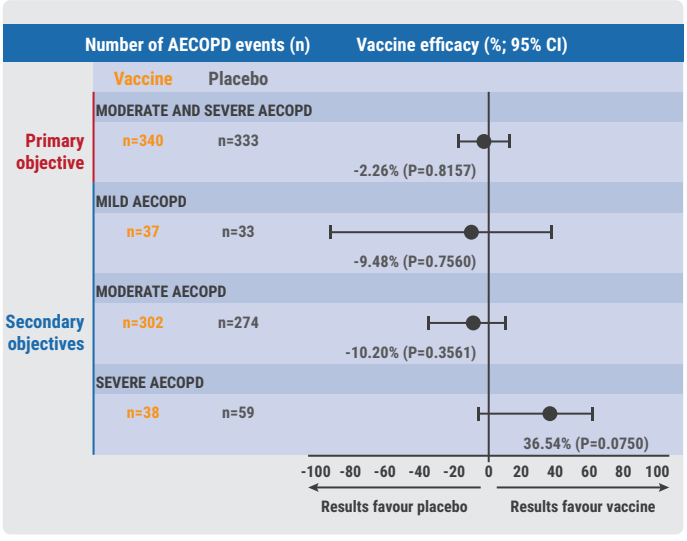
Reduction of COPD severe acute exacerbations by candidate vaccine

The presented study was the first randomised, multicentre, placebo-controlled, observer-blind, phase 2b trial to investigate a candidate vaccine against two commonly detected bacteria in COPD patients. While the study failed to meet the primary endpoint of reducing moderate and severe acute exacerbations, a significant reduction of 37% was found for severe acute exacerbations in COPD.

COPD is a leading cause of death worldwide. An increase of 17.5% was seen in deaths in 2017 compared with 2007. Despite progress in the vaccination field, a vaccine against the most frequently detected bacteria associated with acute exacerbation in COPD patients has not been licensed yet. Acute exacerbations in COPD are heterogenous in nature. Bacterial infections with non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat) are frequently associated with acute exacerbations. Prof. Stefan Andreas (Gastarzt Abteilung Pneumologie der Medizinischen Klinik II Gießen, Germany) and his team have been investigating a candidate NTHi-Mcat vaccine containing bacterial surface proteins [1]. The aim of the current randomised, placebo-controlled, observer-blind, multicentre trial was to investigate whether vaccination reduces the number of exacerbations in patients with COPD. In the trial, 67 sites were recruiting patients, mainly in Europe but also in the United Kingdom and the United States. The most important inclusion criterium was having at least 1 moderate or severe acute exacerbation of COPD in the last 12 months. Patients were randomised to receive placebo or the vaccine containing NTHi and Mcat antigens combined with a liposome-based adjuvant, added to create a stronger immune response. Two intermuscular injections of vaccine or placebo were given 60 days apart. Sputum and blood samples were collected for immunogenicity assessment. Quantitative PCR was done to detect bacteria in sputum. The primary outcome of the study was the rate of moderate or severe exacerbations 1 year after the vaccination period, starting 1 month after the 2-dose vaccination.

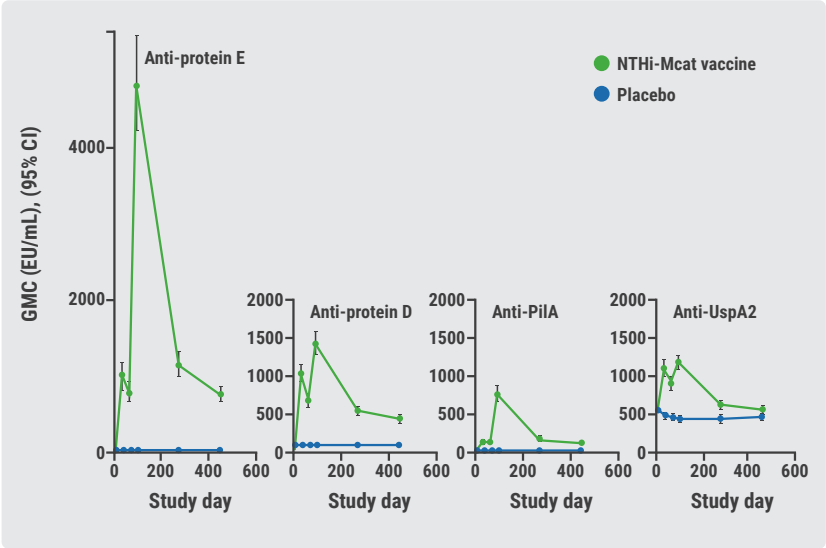
In total, 673 COPD patients were included in the study: 340 patients in the vaccine group and 333 patients in the placebo group. No vaccine efficacy was shown for moderate and severe acute exacerbations of COPD, mild acute exacerbations of COPD, and moderate acute exacerbations of COPD (P=0.83, P=0.76, P=0.37, respectively; see Figure 1). However, severe acute exacerbations of COPD (n=38 vaccine group; n=59 control group) were reduced by 36.7% (P=0.07).

Figure 1: Vaccine efficacy data [1]



No safety concerns were identified. Only a small number of severe adverse events and no vaccine-related serious adverse events were reported. Local adverse events as mild pain,

Figure 2: Vaccine immunogenicity data [1]



People with respiratory conditions like COPD have been at increased risk during the COVID-19 pandemic. COVID-19 measures have had a big impact on the diagnosis and follow-up of respiratory diseases. Decreases and delays in identifying new cancers and delivery of treatment will increase morbidity and mortality for years to come. The aim of the presented study was to evaluate possible differences in the discharge diagnosis of older patients with COPD with known lung cancer, first diagnosis of lung cancer, and lower respiratory tract infections (LRTI) [1]. Data from pre-pandemic (2019) was compared with data from during the pandemic (2020).

redness and/or swelling at the injection side were common. Immunogenicity results showed that the candidate vaccine induced an antigen-specific immune response (see Figure 2).

Taken together, the primary endpoint of reducing the frequency of moderate and severe acute exacerbations of COPD was not met. However, immunogenicity and vaccine efficacy data looked promising as a reduction of severe acute exacerbations of COPD was demonstrated. The presented study was the first randomised controlled trial to investigate a vaccine against two frequently detected bacteria in COPD patients. The data may encourage further investigation of the candidate NTHi-Mcat vaccine.

1. Andreas S, et al. Late Breaking Abstract - First-time assessment of efficacy of candidate vaccine to prevent acute exacerbations of chronic obstructive pulmonary disease (AECOPD): multicentre, randomised, controlled, observer-blind phase 2b trial. Abstract 210. ERS 2021, 5–8 September.

The effect of the pandemic on the discharge diagnosis of older COPD patients

Differences in discharge diagnosis of COPD patients were compared before and during the COVID-19 pandemic. Less respiratory tract infections (RTIs) were observed during the pandemic due to social distancing measures. More complications related to lung cancer were seen because of inadequate monitoring of the disease. In addition, more patients were diagnosed with lung cancer during the pandemic, which were mainly from lower socioeconomic classes.

In total, 514 patients were included who were admitted in 2019 and 464 patients in 2020. The mean age was 70 years. In 2020, more patients (54/76, 71%) came from underdeveloped areas compared with 2019 (P<0.01).

Table: Discharge diagnosis before (2019) and during (2020) the COVID-19 pandemic [1]

Diagnosis	2019 (n=514)	2020 (n=464)
Complications related to known lung cancer	30 (5.8%)	45 (9.6%)
First diagnosis of lung cancer	22 (4.2%)	76 (16.3%)
Lower respiratory tract infections	124 (24.2%)	104 (22.4%)

In 2020, fewer patients with an LRTI were admitted compared with 2019 (see Table). In contrast, more patients were diagnosed with lung cancer in 2020 and more complications were seen in patients with known lung cancer in 2020 versus 2019.

To conclude, differences in discharge diagnosis could have been related to COVID-19 measures like quarantine and lack of monitoring of disease progression. Moreover, patients from lower socioeconomic classes had less adequate access to the public healthcare system in 2020 than in 2019.

1. Dodos K, et al. Late Breaking Abstract - Preliminary results in differences between elderly COPD patients admitted in a COVID-19 free respiratory ward before and during the pandemic. Abstract 105. ERS 2021, 5–8 September.

Paediatrics and Vaccinology

Lower influenza vaccination coverage in children with chronic conditions

More information on coverage of mandatory and highly recommended vaccines would help to optimise care for patients at risk. The presented study showed that children with asthma had lower influenza vaccination rates than children with cystic fibrosis, while being at higher risk for severe influenza-associated complications. This difference was seen despite physicians' vaccination counselling.

Recent literature has reported on poor influenza vaccination rates in children with chronic diseases. However, little is known about specific data for children with asthma and cystic fibrosis. Therefore, the current study assessed the seasonal influenza vaccination coverage level for the 2020–2021 season compared with the routine vaccination coverage [1].

Paediatric patients older than 6 months diagnosed with asthma or cystic fibrosis were included in the study that took place in a respiratory clinic in Greece. Parents were asked to fill in a questionnaire and to share the vaccination status. Telephone interviews were held to gather information on withdrawal of vaccination. The study was performed from October to December 2020.

Participants were children with cystic fibrosis (n=63) and asthma (n=41) with a mean age of 14.3 and 12.3 years, respectively. Slightly more boys (54%) than girls were included. The influenza vaccination rate for cystic fibrosis was 94% compared with 59% for asthma (P<0.05). The vaccination rates for routine vaccines were higher: 100% of asthma patients were vaccinated against hepatitis B, DTPCaHi, conjugate pneumococcal, and measles, mumps, and rubella. Of cystic fibrosis patients, 73% were vaccinated with the polysaccharide pneumococcal vaccine. Parents reported to have been informed by clinicians about the vaccination recommendations, including the influenza vaccine, in 96% of cystic fibrosis and 83% of asthma patients.

In short, despite physicians' vaccination counselling, a significant difference was found in the seasonal influenza vaccine coverage between cystic fibrosis and asthma patients. More research is needed to understand motivators and barriers to vaccinate children with chronic respiratory disease.

1. Hatziagorou E, et al. Influenza vaccination in children with high-risk chronic diseases. Abstract 3146. ERS 2021, 5–8 September.

Better lung function in children with a healthy diet

A healthy diet in mid-childhood, including fish, fruits, vegetables, and nuts, was associated with better lung function. Aiming for consuming a varied diet, fewer processed foods, and more plants, should be considered as a healthy approach for children to keep their lungs happy.

Previous studies have shown associations between dietary patterns and lung function in adults. For example, the Mediterranean diet has been associated with beneficial health effects. However, data on the relationship of food and lung function in children is scarce. Lung function in childhood is particularly important, because in childhood maximum lung function is being developed which has a life-long impact. Dietary patterns are the combined effects of all foods consumed. Two main approaches for characterising dietary patterns are commonly used: empirical methods and *a priori* indices. Dr Mohammad Talaei Pashiri (Queen Mary University of London, UK) and his team investigated whether 3 distinct dietary patterns in mid-childhood were associated with lung function in adolescence in the longitudinal ALSPAC study [1].

A birth cohort in Bristol, UK, was used for the current analysis. The study identified 3 dietary patterns: 'junk', 'traditional', and 'health-conscious'. Junk food was a synonym for processed food, including white bread, sweets, cakes, ice cream, and chocolate, among others. Traditional food included poultry, red meat, vegetables, fish, and rice. Health-conscious food had overlap with traditional food regarding fish, vegetables, and rice, but also included vegetarian options, nuts, and fruit. Parents were asked to fill out food frequency questionnaires when their child reached the age of 7 years. At 15.5 years of age, lung function was measured.

The primary outcome was lung function measurements transformed to z-scores based on the Global Lung Function Initiative (GLI) curves. The primary outcome was adjusted for age, height, ethnicity, and sex. Multivariable linear regression analysis was performed and the model was adjusted for potential confounders, including demographics, urban/rural, parental history of atopic disease, maternal smoking, siblings, physical activity, and total energy intake. In addition, potential mediators were considered, including vitamins, minerals, and adiposity.

In total, 14,541 mothers were asked to participate in the original study. Of these mothers, 8,035 completed diet data. Around 3,500 lung function assessments were done. Post-bronchodilator lung function measures were done in 3,085 children. In the participating children, the health-conscious pattern was associated with higher FVC (P=0.006) and FEV_1 levels (P=0.02; see Table). Conversely, the junk food pattern was associated with significant lower levels of FVC (P=0.009) and FEV_1 (P=0.04).

Table: Linear regression coefficients for lung function measures (z scores) according to quartiles of dietary pattern scores, adjusted for potential confounders [1]

	Quartiles of dietary pattern score				
	Q1	Q2	Q3	Q4	P-value
Health-conscious					
FVC	0.00	0.09 (-0.04–0.23)	0.10 (-0.04–0.23)	0.21 (0.06–0.36)	**0.006**
FEV_1	0.00	0.09 (-0.05–0.23)	0.11 (-0.03–0.26)	0.19 (0.04–0.35)	**0.02**
FEF_{25-75}	0.00	0.08 (-0.04–0.20)	0.06 (-0.06–0.18)	0.11 (-0.02–0.25)	0.13
Junk					
FVC	0.00	0.01 (-0.12–0.13)	-0.08 (-0.22–0.05)	-0.20 (-0.36–0.04)	**0.009**
FEV_1	0.00	0.03 (-0.10–0.16)	-0.06 (-0.20–0.08)	-0.16 (-0.43–0.01)	**0.04**
FEF_{25-75}	0.00	0.01 (-0.10–0.12)	-0.03 (-0.15–0.09)	-0.06 (-0.20–0.08)	0.38

Significant P-values in bold. Green colours show a positive association; red colours show a negative association.

No association was found for traditional dietary pattern and lung function. In addition, no effect of mediation was found for vitamins, minerals, and adiposity. However, zinc partially explained the negative association between the junk food pattern and FVC.

In conclusion, a healthier diet was associated with higher subsequent lung function, while a diet high in processed food was associated with lower lung function.

1. Talaei Pashiri M, et al. Dietary patterns and lung function in childhood: A longitudinal study. Abstract 2960. ERS 2021, 5–8 September.

Impaired response to pneumococcal vaccine in children with recurrent respiratory infections

Paediatric patients with recurrent respiratory infections (RRI) and/or chronic cough (CC) have a higher incidence of impaired response to the 13-valent pneumococcal conjugate vaccine (PCV13) compared with the general population. Booster vaccination may be recommended for this patient group.

While most healthy infants and children develop antibodies to the majority of serotypes included in PCV13, children with immunodeficiencies are known for their impaired response. Functional antibodies (FAB) tests measure specific IgG against vaccines to diagnose deficiencies and can be used to evaluate clinical responses to vaccination. The current study examined the incidence of impaired PCV13 response in children with RRI and/or CC referred to a tertiary paediatric respiratory centre compared to the general population [1].

A retrospective review was performed of patient notes of children between the age of 2 and 15 years with a relevant history of RRI and/or CC that were referred to the paediatric clinic and had FAB testing in a previous 2-year period (between January 2018 and December 2019).

Data of 137 patients was included. Most children were male (53.3%), and the mean age was 5.9 years. Of patients included, 100 (73%) had a history of RRI, 105 (76.6%) had a history of CC, and 68 (49.6%) had a history of both RRI and CC. All patients were identified with RRI and/or CC during a previous FAB test 2 years previously. Asthma and preschool wheeze were frequently identified (37% and 42%, respectively).

A specific antibody concentration of 0.35 µg/mL or higher to <7 PCV13 serotypes was considered to be an impaired response. Of 137 patients, 45 (33%) had an impaired response to PCV13. Children on moderate or high dose of inhaled corticosteroids were more likely to have an impaired response (OR 2.8; 95% CI 0.94–7.77). Patients on regular azithromycin were also more likely to have an impaired response (OR 1.51; 95% CI 0.53–4.27).

Conclusively, paediatric patients referred to tertiary centres with RRI or CC have a high incidence of an impaired response to PCV13 compared to the general population. Children who fail to develop an immune response against PCV13 might be considered for a booster dose.

1. Elashmawy M, et al. Impaired response to 13-valent pneumococcal conjugate vaccine (PCV13) in children with recurrent respiratory infections and chronic cough. Abstract 3150. ERS 2021, 5–8 September.

Need for validated severity score in the assessment of bronchiolitis

Bronchiolitis is a major cause of illness and hospitalisation in infants. Several bronchiolitis scores that are currently used for patient assessment and research purposes lack validation and reliability. A systematic review demonstrated the need for a new, validated severity score.

Bronchiolitis is the most common cause of hospitalisation in children under 2 years of age. However, most infants with bronchiolitis are not hospitalised. In the United Kingdom, 1 to 3% of infants are hospitalised with bronchiolitis, of which around 10% need critical care. Clinical conditions can change quickly, particularly when patients suffer from apnoea. A severity score for bronchiolitis can be helpful to aid clinical decision making as well as an outcome measure for research studies.

Mr William Bedson (University of Liverpool, UK) and colleagues conducted a systematic review in which they aimed to identify new or modified severity scores used for the assessment of bronchiolitis [1]. The secondary aim was to evaluate items commonly used within these scores, followed by the tertiary aim to assess validity and reliability data for these scores.

The systematic review protocol was PROSPERO registered (CRD42020218816). MEDLINE, CINAHL, PubMed, Embase databases were searched using relevant terms. Titles, abstracts, and full texts were screened by two reviewers using predetermined inclusion and exclusion criteria: all types of studies except systematic reviews, children aged <2 years with bronchiolitis, and all languages and years of publications. Data extraction included study characteristics, items within score, and any associated validity and reliability data.

In total, 52 scores were identified, reported between 1973–2019, including 30 original and 22 modified scores. Most scores were administered in emergency departments (n=27). Authors assessed 51 different items and grouped them into 9 domains. Most common items were respiratory rate (88%), wheeze (83%), muscle retractions (71%), nasal flaring (42%), and oxygen saturation (32%). The previously mentioned items were reviewed in more depth. Validity and reliability data was available in 15 studies.

There are many scores currently cited for use in bronchiolitis assessment, which most commonly involve assessments of respiratory rates, wheeze, and retractions. Most scores were poorly validated. Mr Bedson ended his presentation sharing that there is an urgent need for development of a well validated severity score for bronchiolitis.

1. Bedson W, et al. Severity Scores used in the assessment of Bronchiolitis: A systematic review. Abstract 2846. ERS 2021, 5–8 September.

No immunological parameters identified for Down syndrome children

It is known that children with Down syndrome suffer more from frequent infections than the general population. Parameters that are predictive of recurrent respiratory tract infections (RRTIs) can be helpful in guiding treatment. The current study aimed to identify blood parameters associated with RRTI, but failed in finding any.

Children with Down syndrome have an increased risk of infections and especially RRTIs due to predisposing factors, both anatomical and physiological ones. Immunological deviations have been described in literature before, including decreased white blood cell (WBC) count, decreased total lymphocyte count, and disturbances in levels of immunoglobulins (Igs). However, the clinical relevance of these aberrations has been unstudied. The aim of the presented study was to compare immunological parameters in Down syndrome children with and without RRTIs with the purpose of identifying values that are predictive for RRTIs in this patient population [1].

A prospective, cross-sectional study was conducted. Children with Down syndrome aged 0 to 18 years were included and stratified based on having RRTIs. Blood samples were collected annually from the cohort determining WBC count and differentiation, lymphocyte subsets, and IgA, IgG, and IgM levels. Additionally, data on infectious burden was collected from patient files.

In total, 69 Down syndrome children were included in the study: 27 with RRTI and 42 without RRTI. Age and gender were equally distributed. The mean age at sampling was 6.3 years. No statistically significant difference was found between the RRTI versus no RTTI group after correction for age. Differences, however not statistically significant, were found for WBC count (P=0.074), neutrophil count (P=0.051), and ratio CD4+/CD8+ cells (P=0.076). Logistic regression showed poor clinical value and poor predictors for RRTI. In the complete Down syndrome cohort, more children with lower total WBC, lymphocytes, Th cells, B cells, IgM, and higher IgG were identified.

No parameter that clearly correlates with RRTIs could be found. Therefore, the authors suspected the higher infectious burden found in Down syndrome children to be multifactorial in origin. Future studies should focus on larger study populations, and should include control groups. In addition, possible confounders should be minimalised, such as airway anomalies.

1. De Lausnay M, et al. Immunological parameters in Down syndrome in children with and without recurrent lower respiratory tract infections. Abstract 3156. ERS 2021, 5–8 September.

Increased impact of air pollution on lung function in preterm infants

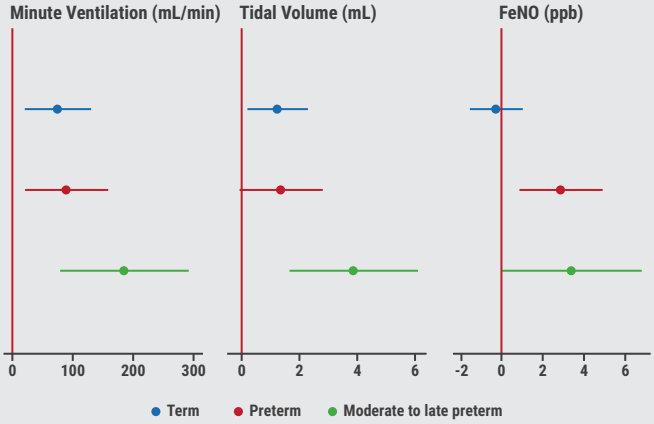
Infants of mothers who are exposed to higher air pollution during pregnancy may have reduced lung function development. The presented study showed that significant negative associations during the second trimester of pregnancy were found between air pollution and postnatal lung function. Preterm infants showed significant higher susceptibility to air pollution exposure, leading to impaired postnatal lung function.

Infants born prematurely have impaired capacity to deal with oxidative stress shortly after birth. Particulate matter with a diameter >10 µm (PM_{10}) and NO_2 are known oxidative stressors to airways and lungs. Therefore, Ms Fabienne Decrue (University of Basel, Switzerland) and colleagues investigated whether preterm infants are more susceptible to pre- and postnatal exposure to air pollution in comparison to term infants, and if this is reflected in altered postnatal lung function [1,2].

Infants from the Basel-Bern infant lung development (BILD) cohort born between 1999–2017 were included. Individual air pollution (expressed in PM_{10} and NO_2) exposure was calculated individually for each infant during the second trimester of pregnancy and postnatal. The primary outcome was postnatal lung function at 33 weeks postconceptional age, expressed as tidal breathing flow volume loops and exhaled surrogate markers of inflammation, and oxidative stress response (fractional exhaled nitrogen oxide, FeNO).

Within this study, 771 infants were included over a period of 18 years, of which one third were preterm infants (n=254). Preterm infants were divided over 2 groups: moderate-to-late preterm infants (32–37 weeks) and extreme preterm infants (<31 weeks). Significant associations of increases in PM_{10} during pregnancy were found for minute ventilation, tidal volume, and FeNO (see Figure). Associations of air pollution and FeNO differed significantly between preterm and term infants (P=0.006).

Figure: Lung function as a result of PM10 [1]



Ms Decrue was able to show that prenatal exposure to air pollution, especially during the second trimester of pregnancy, was associated with impaired infant lung function. Moreover, it was demonstrated for the first time that enhanced effects in preterm infants are suggestive of an amplified susceptibility indicating that air pollution measures should be taken to prevent populations at risk, even in low-to-moderate polluted areas such as Switzerland.

1. Decrue F, et al. Increased impact of air pollution on lung function in preterm vs. term infants: the BILD study. Abstract 2958. ERS 2021, 5–8 September.
2. Decrue F, et al. Am J Respir Crit Care Med. 2021 Sep 29.

Pearls in Asthma Research

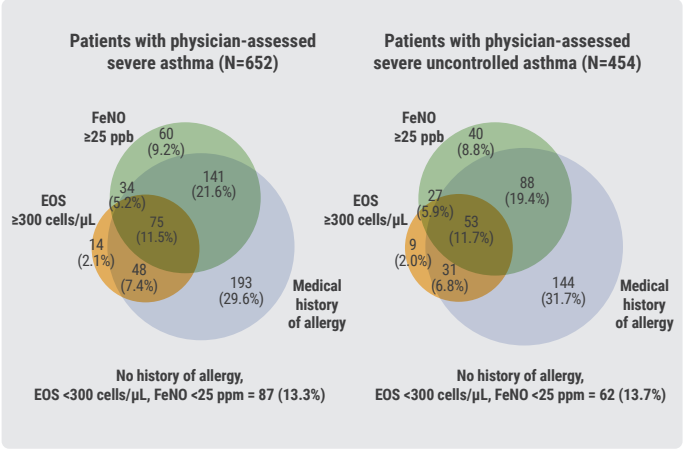
Biomarkers do not discriminate severe from severe uncontrolled asthma

Biomarkers are key to understanding asthma phenotypes and may help in distinguishing patient subgroups to guide therapeutic strategies. In the NOVELTY study, markers such as blood eosinophils, fractional exhaled nitric oxide (FeNO), and atopy history did not distinguish severe asthma from severe uncontrolled asthma.

Asthma is a heterogeneous disease characterised by multiple phenotypes. Phenotype-specific markers could be useful in predicting outcomes and therapeutic response to target therapies. In the previous years, research has been done on the identification of valid biomarkers for asthma. With the NOVELTY study (NCT02760329), Dr Bo Ding (AstraZeneca, Sweden) and colleagues have added a considerable amount of biomarker data to the asthma field [1].

The NOVELTY study is a global, prospective study of patients with physician-assigned asthma. The primary objective was to characterise the distribution of biomarkers (Type 2 inflammatory markers) in severe asthma. Patients who had severe asthma or severe uncontrolled asthma at baseline were included. Physician-classified asthma severity was used, with uncontrolled asthma defined as an asthma control test score <20 or ≥1 exacerbation in the past 12 months. Atopy history was also available. The blood biomarkers of interested were eosinophils and FeNO.

Figure: Distribution of biomarkers in NOVELTY patients with severe asthma and severe uncontrolled asthma [1]



Overall, 652 patients had physician-assessed severe asthma at baseline, and 454 (70%) of these met the criteria for uncontrolled asthma (see Figure). The mean age was 54.0 years for severe asthma and 54.1 years for severe uncontrolled asthma. The overall distribution of Type 2 inflammation markers was similar in patients with severe versus severe uncontrolled asthma. Most patients had ≥1 positive marker (86.7% for severe asthma vs 86.3% for severe uncontrolled asthma). Of patients with severe asthma, 45.7% had ≥2 positive markers, compared to 43.8% of patients with uncontrolled severe asthma. Distribution of all 3 markers was also similar between both groups: 11.5% versus 11.7%. Moreover, 13.3% versus 13.7% of patients were not positive for any of the markers.

Taken together, around 86% of patients with severe asthma had some marker of Type 2 inflammation. Overlap of marker positivity was common: high eosinophils, high FeNO, and history of allergy were similar among NOVELTY patients with severe asthma and severe uncontrolled asthma.

1. Ding B, et al. Distribution of biomarkers in severe asthma and severe uncontrolled asthma. Abstract 4214. ERS 2021, 5–8 September.

Increased blood neutrophiles in patients with obesity and asthma

Understanding the underlying mechanisms of adult-onset asthma and identifying risk factors may extend the knowledge of pathophysiology and medication response, leading to a better treatment approach. The presented study showed that blood neutrophils were increased in patients with severe obesity and asthma.

It is known that obesity is an important risk factor for adult-onset asthma. "However, the association between obesity and markers of inflammation in this patient group has not been intensively studied," Dr Helena Backman (Umea University, Sweden) explained during her presentation [1].

The aim of the current study was to investigate the association between obesity and inflammatory markers in adult-onset asthma. Since 1985, blood samples have been collected within different population-based studies in Northern Sweden. In 2019–2020, previous participants were invited to follow-ups including structured interviews,

spirometry, measurements of exhaled nitric oxide (FeNO), skin prick testing, blood samples, and BMI. BMI was categorised as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), obesity (30–34.9), and severe obesity (≥35). Inclusion criteria included asthma-onset after 15 years of age.

In total, 251 patients participated in the study with a mean age of 63 years and mean BMI of 29.1. Of these, 0% had underweight, 22% had normal weight, 41% had overweight, 26% had obesity, and 11% severe obesity. Increased mean blood neutrophils ($5.3x10^9$/L) were observed in participants with severe obesity (P<0.001). Of participants with obesity, 83% had blood neutrophils ≥$4x10^9$/L compared with 32% of patients with normal weight. Between BMI categories, atopy, FeNO, and blood eosinophils did not differ significantly. Lower lung function for both FEV_1 and FVC (83% and 82%, respectively) was seen in severe obesity as well.

In conclusion, severe obesity was strongly associated with blood neutrophils in adult-onset asthma. The identification of increased neutrophils in severely obese adults suggested that neutrophils play an essential role in the pathogenesis of obesity-related disease.

1. Backman H, et al. Obesity and inflammatory markers in adult-onset asthma. Abstract 4215. ERS 2021, 5–8 September.

Dynamics of environmental pollution during and after COVID-19 lockdown

COVID-19 lockdowns caused global air pollution declines because of an unprecedented reduction in economic and transport activity. After the relaxation of COVID-19 measures, the environmental pollution has increased again leading to more oxidative stress and systemic inflammation in healthy individuals.

COVID-19-related lockdown resulted in a historic drop in air pollution, that offered a great opportunity to study the effects of air pollutants on human health. The POLCOV study therefore aimed to determine and compare oxidative stress biomarkers and cytokines in healthy individuals during the lockdown and 6 months after easing mobility restrictions in Barcelona [1].

In this prospective study, blood samples were collected during 2 moments from healthy, non-smoking adults. Age, sex, and postal district of residence were collected for all individuals. Blood samples were analysed for eosinophil and Th1/Th2/Th17-related cytokine levels by a multiplex assay. Eotaxin, IFN-γ, IL-7, and RANTES were measured for analysis of regulatory cytokines. In addition, G-CSP, IL-1b, MIP-1α, IL-4, and IL-13 were measured to analyse proinflammatory cytokines. Finally, levels of 8-isoprostane were measured as a biomarker for oxidative stress.

Samples from 58 participants were analysed; mean age was 37 years, most participants were female (62%), and 53% of participants were diagnosed with atopy previously. At the moment of collection of the first sample, the air pollution had been decreased with 80% compared with pre-lockdown. After 6 months, air pollution had reached similar levels to pre-lockdown. At 6 months after the relaxation of COVID-19 restrictions, a significant increase in levels of 8-isoprostane, G-CSF, IL-1β, IL-1ra, IL-4, IL-13, and MIP-1α was found. In contrast, a significant decrease in levels of IFN-γ, TNFα, eotaxin, PDGF-BB, MIP-1β, IL-6, IL-7, and RANTES was observed. No significant differences were observed in the level of eosinophils. Furthermore, levels of other cytokines were not detectable in both periods.

Taken together, biomarkers and cytokines related to oxidative stress and systemic inflammation were found to be significantly increased when environmental pollution increased after easing restrictions due to COVID-19 lockdown.

1. De Homdedeu et al. Late Breaking Abstract - The impact of the reduction of environmental pollution during COVID-19 lockdown on healthy individuals (POLCOV Study). Abstract 3255. ERS 2021, 5–8 September.

Magnesium supplements improved lung function in asthma patients

While there is no specific diet recommendation for asthma, there are some foods and nutrients that may help support lung function and reduce asthma symptoms. The presented study showed that oral magnesium supplements may benefit patients with mild-to-moderate asthma.

Bronchial asthma affects up to 18% of the population worldwide. In addition to asthma medication, diet and nutritional supplements may play a role in controlling the disease. Magnesium is a mineral that could be relevant to asthma because of its potential effects on the bronchial muscles. When given intravenously, it leads to bronchodilation in acute severe asthma. For that reason, the current study was conducted to evaluate the effect of oral magnesium supplements in the control of asthma symptoms and lung function parameters [1].

The authors conducted a prospective, randomised, single-blinded, comparative, parallel group study. Inclusion criteria were age ≥18 years, bronchial asthma diagnosis according to the GINA guidelines, and having asthma under control with medication. Both inpatients and outpatients were eligible. Patients were randomly assigned to receive oral magnesium supplements (400 mg once daily for 4 months) in addition to their regular asthma medication, or their regular asthma medication alone. Both groups were followed at an interval of 4 weeks for 4 months. Evaluated endpoints were Asthma Control Test (ACT) scores, peak expiratory flow rate, lung function by spirometry, and absolute eosinophil count. Moreover, serum magnesium levels were measured every month, and patients were contacted by phone on a weekly basis to evaluate potential magnesium side effects.

A total of 58 patients were included in the study; mean age was 40 years. An equal number of female participants were included in the magnesium group, while slightly more male (51.7%) participants were included in the regular treatment group.

The median change in serum magnesium levels was 0.2 mg/dL after the fourth study visit (P=0.001). No change in serum magnesium was noticed in the regular treatment group. Furthermore, patients in the magnesium group had significantly better ACT scores and FEV_1 levels during the fourth study visit. Overall, the study showed improved lung function and asthma control on oral magnesium supplements compared with conventional therapy in patients with mild to moderate asthma.

1. Rowhit Y, et al. A randomised controlled study on effect of oral magnesium supplements in control of symptoms of bronchial asthma and lung function parameters. Abstract 887. ERS 2021, 5–8 September.

Blood inflammatory phenotypes associated with clinical symptoms of asthma

Asthma blood inflammatory phenotypes might be associated with different clinical features. Further identification of these asthma phenotypes could help improve treatment outcomes. The presented study found different associations with clinical symptoms for the neutrophilic and eosinophilic phenotypes.

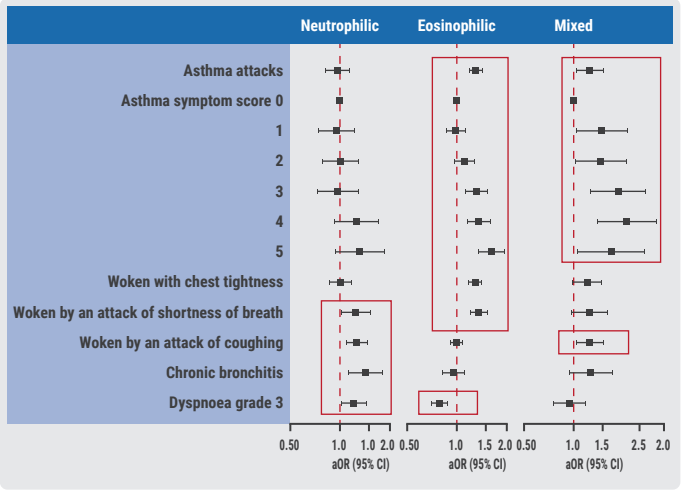
Asthma is a heterogenous disease characterised by various phenotypes, including inflammatory ones. In blood and sputum samples, 4 different phenotypes have been identified based on the results of the Environment of Asthma (EGEA) case control study: eosinophilic, neutrophilic, paucigranulocytic, and mixed phenotypes. Cut-offs of 250 and 500 cells/mm^3 have been suggested for eosinophils and neutrophils, respectively. However, these asthma inflammatory phenotypes have not been verified in population-based studies. Therefore, the current study, presented by Dr Tajidine Tsiavia (University of Paris-Saclcy, France) aimed to identify and characterise the 4 phenotypes in adults from the largest French population-based 'Constances' cohort [1].

From 2012 to 2019, participants aged 18 to 69 years were randomly selected from the database of the National Pension Insurance Fund and invited to participate in the study. Data from questionnaires and white blood cell (WBC) counts at moment of inclusion was analysed. Current asthma was defined by the report of asthma attacks, respiratory symptoms, or use of asthma medication in the past 12 months. Inflammatory phenotypes were defined based on the EGEA cut-offs, as mentioned before. Statistical analyses included logistic regression models adjusted for age, sex, BMI, smoking, education level, French deprivation index, and asthma treatment.

Clinical data was available from 192,648 patients, from which 160,272 patients were selected that matched the inclusion criteria. Of these participants, 15,019 (9.4%) reported current asthma. Phenotypes differed significantly by age, sex, BMI, smoking, education level, and asthma treatment.

The neutrophilic, eosinophilic, and mixed phenotypes were positively associated with several clinical variables (see Figure).

Figure: Associations between inflammatory phenotypes and clinical characteristics of asthma [1]



Positive associations are outlined in red.

The neutrophilic phenotype was associated with being woken by an attack of coughing, chronic bronchitis, and dyspnoea (aOR ranging from 1.21 to 1.42). The eosinophilic and mixed phenotypes were associated with asthma attacks (aOR 1.31; 95% CI 1.20–1.42 and aOR 1.25; 95% CI 1.02–1.53, respectively) and asthma symptom score P<0.001. The eosinophilic phenotype was also associated with being woken with chest tightness (aOR 1.30 95% CI 1.20–1.40). The distribution of asthma phenotypes differed by age (P<0.0001). Data for the paucigranulocytics was not shown.

In conclusion, clinical differences were found between blood inflammatory phenotypes in a large population-based cohort. Similar differences have been described in clinical and case-control studies. Blood inflammatory phenotypes may be helpful in better understanding the pathophysiology of asthma and in guiding treatment.

1. Tsiavia T, et al. Blood inflammatory phenotypes in asthma in the Constances cohort. Abstract 4217. ERS 2021, 5–8 September.