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## COPD

Nihon Hoshasen Gijutsu Gakkai Zasshi

. 2022 Aug 22.

doi: 10.6009/jjrt.2022-1271. Online ahead of print.

# [Quantitative Evaluation of Airway Lesions in Chronic Obstructive Pulmonary Disease by Applying Deep Learning Reconstruction to Ultra-high-resolution CT Images: Correlation between Wall Area Percentage and Forced Expiratory Volume in One Second Percentage]

[Article in Japanese]

Shun Muramatsu[1], Kazuhiro Sato[2]

Affiliations expand

- PMID: 35989253

- DOI: 10.6009/jjrt.2022-1271

# Abstract

**Purpose:** Using ultra-high-resolution images reconstructed with the Advanced intelligent Clear-IQ Engine (AiCE) lung to measure wall area percentage (WA%), we demonstrated that WA% measured in more distal bronchus has a stronger correlation with respiratory function ($FEV_1$%). Furthermore, we also demonstrated that WA% measured from images with the higher spatial resolution has a stronger correlation with $FEV_1$%.

**Methods:** The modulation transfer function (MTF) and noise power spectrum (NPS) of the ultra-high-resolution images reconstructed by the AiCE body and the AiCE lung were compared. In addition, WA% from the first- to seventh-generation bronchus was measured for B1 and B10 in the right lung from clinical images obtained with the two reconstruction methods, and the correlation coefficients with $FEV_1$% were evaluated.

**Results:** The MTF was more superior for the AiCE lung than for the AiCE body, and the NPS was lower for the AiCE lung than for the AiCE body in the low-frequency region. The correlation between WA% and $FEV_1$% was slightly stronger in the AiCE lung than in the AiCE body.

**Conclusion:** This study showed that WA% measured from the 7th-generation bronchus using ultra-high-resolution images reconstructed with the AiCE lung strengthens the correlation with $FEV_1$%. Furthermore, the higher the spatial resolution of the measurement images, the stronger the correlation between WA% and $FEV_1$%.

**Keywords:** chronic obstructive pulmonary disease; deep learning reconstruction; forced expiratory volume in one second percentage; high-resolution image; wall area percentage.

SUPPLEMENTARY INFO

Publication typesexpand

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BMC Pulm Med

. 2022 Aug 20;22(1):320.

doi: 10.1186/s12890-022-02114-8.

# The association between leukocyte telomere length and chronic obstructive pulmonary disease is partially mediated by inflammation: a meta-analysis and population-based mediation study

Tieshan Wang[#1], Zhaoqi Jia[#2], Sen Li[#3], Yuxin Li[2], Tingting Yu[2], Tao Lu[2], Yuanyuan Shi[4,5]

Affiliations expand

- PMID: 35987624

- DOI: 10.1186/s12890-022-02114-8

## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is one of the major health issues worldwide. Pathophysiological changes in COPD are mainly reflected in the deterioration of lung function with aging.

**Methods:** Considering that telomere length is a hallmark of biological aging, we first performed a meta-analysis to summarize the current knowledge about the relationship between telomere length and COPD and then employed individual-level data from the continuous National Health and Nutrition Examination Survey (NHANES) to investigate whether telomere length could reflect accelerated aging in COPD and serve as an independent predictor. A mediation study was further performed to examine whether the association between telomeres and COPD could be mediated by inflammation, as one of the most important etiologies and characteristics of COPD.

**Results:** The four studies included in our meta-analysis were with high heterogeneity ($I^2$ = 95.7%, $P_{het}$ < 0.001), and the pooled relative risk for COPD comparing the shortest tertile versus the longest tertile was 4.06 (95% CI = 1.38 to 11.96). Of the 6,378 subjects in the

individual-level data analyses using NHANES, 455 were diagnosed with COPD, and multivariable-adjusted logistic regression also indicated that short telomere length was associated with COPD. Consistently, cubic regression spline analyses showed that long telomeres exhibited a significant association with a decreased risk of COPD. In the subsequent mediation analyses, C-reactive protein concentration, white blood cells count and blood neutrophil count, as inflammatory biomarkers, showed a significant indirect effect on the relationship between telomere length and COPD.

**Conclusion:** Accelerated aging in COPD could be characterized by excessive telomere shortening, and inflammatory response might be involved in the underlying mechanisms of COPD pathogenesis promoted by short telomere length. Telomere length measurement may facilitate clinical translational research and targeted therapy of COPD.

**Keywords:** COPD; Inflammation; Mediation study; NHANES; Telomere length.

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- 59 references

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3

Expert Opin Pharmacother

. 2022 Aug 19.

doi: 10.1080/14656566.2022.2116274. Online ahead of print.

# Pharmacotherapy considerations for morning symptoms in chronic obstructive pulmonary disease

Clarus Leung[1], Don D Sin[2]

Affiliations expand

- PMID: 35986503

- DOI: 10.1080/14656566.2022.2116274

## Abstract

N/A.

**Keywords:** chronic obstructive pulmonary disease; circadian rhythm; long-acting bronchodilators.

Proceed to details

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PLoS One

. 2022 Aug 19;17(8):e0273437.

doi: 10.1371/journal.pone.0273437. eCollection 2022.

# Elevated risk of acute epiglottitis in patients with chronic obstructive pulmonary disease: A nationwide cohort study

Shu-Yi Huang[1], Cheng-Ming Hsu[2], Yao-Hsu Yang[3,4], Yuan-Hsiung Tsai[5], Ming-Shao Tsai[2], Geng-He Chang[2], Chia-Yen Liu[3], Yi-Chan Lee[6], Ethan I Huang[2], Yao-Te Tsai[2]

Affiliations expand

- PMID: 35984835

- PMCID: PMC9390908

- DOI: 10.1371/journal.pone.0273437

# Abstract

**Objective:** In individuals with epiglottitis, chronic obstructive pulmonary disease (COPD) is a common comorbidity; however, the impact of COPD under such circumstances is not well documented. Therefore, we performed this population-based study to determine whether, in adults, COPD is a risk factor for epiglottitis.

**Methods:** In this retrospective matched-cohort study, data obtained from the Taiwan National Health Insurance Research Database were analyzed. We identified all patients newly diagnosed as having COPD in 2000-2011 and performed frequency matching and propensity-score matching for every patient with COPD individually to another patient without a COPD diagnosis. We used epiglottitis occurrence as the study endpoint, and we investigated the hazard ratio of epiglottitis by using the Cox proportional hazards model after adjustment for potential confounders.

**Results:** In the frequency matching, the cumulative epiglottitis incidence was significantly higher ($p = 0.005$) in the COPD cohort. According to the adjusted Cox proportional hazard model, COPD exhibited a significant association with elevated epiglottitis incidence (adjusted hazard ratio: 1.76; 95% confidence interval: 1.15-2.70, $p = 0.009$). Similar trend was observed in the propensity-score matching analysis (adjusted hazard ratio: 1.50; 95% confidence interval: 0.99-2.29, $p = 0.057$). Our subgroup analysis revealed COPD to be an epiglottitis risk factor in male patients and those aged 40-64 years.

**Conclusions:** This is the first nationwide matched-cohort research to examine the association of COPD with epiglottitis. Our results revealed that COPD may be a potential risk factor for epiglottitis; thus, clinicians should be mindful of the potential increased risk of epiglottitis following COPD.

## Conflict of interest statement

The authors declare no conflicts of interest.

- 50 references
- 2 figures

SUPPLEMENTARY INFO

Grant supportexpand

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ERJ Open Res

. 2022 Aug 15;8(3):00141-2022.

doi: 10.1183/23120541.00141-2022. eCollection 2022 Jul.

# Real-life burden of hospitalisations due to COPD exacerbations in Spain

José Luis Izquierdo[1,2], José Miguel Rodríguez[1,3], Carlos Almonacid[4], María Benavent[5], Ramón Arroyo-Espliguero[6], Alvar Agustí[7]

Affiliations expand

- PMID: 35983537

- PMCID: PMC9379352

- DOI: 10.1183/23120541.00141-2022

## Abstract

**Background:** Patients with chronic obstructive pulmonary disease (COPD) often suffer episodes of exacerbation of symptoms (ECOPD) that may eventually require hospitalisation due to several, often overlapping, causes. We aimed to analyse the characteristics of patients hospitalised because of ECOPD in a real-life setting using a "big data" approach.

**Methods:** The study population included all patients over 40 years old with a diagnosis of COPD (n=69 359; prevalence 3.72%) registered from 1 January 2011 to 1 March 2020 in the database of the public healthcare service (SESCAM) of Castilla-La Mancha (Spain) (n=1 863 759 subjects). We used natural language processing (Savana Manager version 3.0) to identify those who were hospitalised during this period for any cause, including ECOPD.

**Results:** During the study 26 453 COPD patients (38.1%) were hospitalised (at least once). Main diagnoses at discharge were respiratory infection (51%), heart failure (38%) or pneumonia (19%). ECOPD was the main diagnosis at discharge (or hospital death) in 8331 patients (12.0% of the entire COPD population and 31.5% of those hospitalised). In-hospital ECOPD-related mortality rate was 3.11%. These patients were hospitalised 2.36 times per patient, with a mean hospital stay of 6.1 days. Heart failure was the most frequent comorbidity in patients hospitalised because of ECOPD (52.6%).

**Conclusions:** This analysis shows that, in a real-life setting, ECOPD hospitalisations are prevalent, complex (particularly in relation to heart failure), repetitive and associated with significant in-hospital mortality.

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## Conflict of interest statement

Conflicts of interest: All authors declare no conflicts of interest.

- 36 references
- 1 figure

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Eur J Intern Med

. 2022 Aug 15;S0953-6205(22)00289-8.

doi: 10.1016/j.ejim.2022.08.011. Online ahead of print.

# Inhaled triple therapy in individuals with Chronic Obstructive Pulmonary Disease and indications of pulmonary rehabilitation

Michele Vitacca[1], Mara Paneroni[2], Antonio Spanevello[3], Piero Ceriana[4], Nicolino Ambrosino[5]

Affiliations expand

- PMID: 35981915

- DOI: 10.1016/j.ejim.2022.08.011

*No abstract available*

**Keywords:** Dyspnoea; Exercise tolerance; Exercise training; Health status; Long-acting bronchodilation.

SUPPLEMENTARY INFO

Publication typesexpand

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Diabetol Metab Syndr

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. 2022 Aug 16;14(1):115.

doi: 10.1186/s13098-022-00887-w.

# MAFLD associated with COPD via systemic inflammation independent of aging and smoking in men

Tsubasa Tsutsumi[1], Dan Nakano[2], Machiko Kawaguchi[2], Ryuki Hashida[3], Shinobu Yoshinaga[4], Hirokazu Takahashi[5], Keizo Anzai[5], Takumi Kawaguchi[2]

Affiliations expand

- PMID: 35974418

- PMCID: PMC9380323

- DOI: 10.1186/s13098-022-00887-w


# Abstract


**Background and aim:** Metabolic dysfunction and associated systemic inflammation are risk factors for chronic obstructive pulmonary disease (COPD) and COPD is highly prevalent in men. We investigated the impact of metabolic-associated fatty liver disease (MAFLD) and MAFLD-related systemic inflammation on COPD in men.

**Methods:** We enrolled 2,041 men with fatty liver. Patients were classified into the COPD (n = 420/2041) and non-COPD (n = 1621/2041) groups. COPD and its high-risk group were diagnosed using the Japanese Respiratory Society Disease statement. Systemic inflammation was evaluated using the C-reactive protein (CRP)/albumin ratio. Independent factors for COPD were investigated by multivariate analysis and decision-tree analysis.

**Results:** The prevalence of MAFLD was significantly higher in the COPD group than in the non-COPD group. In multivariable analysis, in addition to heavy smoking and aging, MAFLD was identified as an independent factor for COPD (OR 1.46, 95% CI 1.020-2.101, P = 0.0385). Decision-tree analysis showed that MAFLD, rather than heavy smoking, was the most influential classifier for COPD in non-elderly men (14% in MAFLD vs 6% in non-MAFLD groups). MAFLD was also the second most influential factor in elderly men who were not heavy smokers. In both groups, the CRP/albumin ratio was the first classifier for COPD (16% in the high CRP/albumin ratio group vs 3% in the low CRP/albumin ratio group of non-elderly men).

**Conclusions:** MAFLD is an independent predictor of COPD in men. MAFLD had a significant impact on COPD through systemic inflammation in men of all ages who were not heavy smokers. MAFLD may be useful to broadly identify COPD in men.



**Keywords:** CRP/albumin ratio; Chronic obstructive pulmonary disease; Metabolic associated fatty liver disease; Steatosis; Systemic inflammation.



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## Conflict of interest statement

The authors declare no competing interests.


- 50 references

- 4 figures

SUPPLEMENTARY INFO

Grant supportexpand

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8

Respir Res

. 2022 Aug 16;23(1):208.

doi: 10.1186/s12931-022-02133-3.

# SINFONIA study protocol: a phase II/III randomised controlled trial examining benefits of guided online group singing in people with chronic obstructive pulmonary disease and interstitial lung disease and their carers

Natasha Smallwood[1,2], Amy Pascoe[3], Sara Vogrin[4], Jennifer Philip[5,6]

Affiliations expand

- PMID: 35974347

- PMCID: PMC9380685

- DOI: 10.1186/s12931-022-02133-3

# Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) and interstital lung disease (ILD) are incurable conditions characterised by airflow limitation, persisting respiratory symptoms, and progressive respiratory failure. People living with COPD or ILD often suffer from chronic and severe breathlessness, with limited treatment options and low engagement rates with current therapies. Group singing represents a potential community-based therapy to improve quality of life for patients with COPD or ILD and breathlessness.

**Methods:** This protocol papers describes SINFONIA, a parallel, double-arm, randomised, blinded-analysis, mixed-methods phase II/III trial of guided, online group singing that will be conducted over 24 months. Adults with confirmed COPD or ILD, on stable treatment for at least four weeks at time of recruitment, with a modified Medical Research Council (mMRC) dyspnoea score of two or greater, who are capable and willing to give consent, and not currently participating in pulmonary rehabilitation will be eligible to participate. Carers may optionally enrol in the trial. Data will be collected on quality of life, anxiety and depression, breathlessness, mastery of breathing, exercise tolerance, loneliness, healthcare utilisation, and carer quality of life (optional). Participants will be randomised 1:1 to intervention or control arms with intervention arm attending one 90 min, guided, online, group singing session per week for 12 weeks and control arm continuing routine care. Phase II of the trial aims to determine the feasibility and acceptability of guided, online group singing and will collect preliminary data on effectiveness. Phase III aims to determine whether guided, online group singing has an effect on quality of life with the primary outcome being a between arm difference in quality of life (36-item Short Form Survey) measured at 12 weeks.

**Discussion:** SINFONIA is the first study is the first of its kind in Australia and to our knowledge, the first to deliver the singing intervention program entirely online. Determining the feasibility, acceptability, and effectiveness of guided, online group singing is an important step towards improving low-cost, low-risk, community-based therapeutic options for patients living with COPD or ILD and breathlessness.

**Trial registration:** Phase II- ACTRN12621001274864 , registered 20th September 2021; Phase III- ACTRN12621001280897 , registered 22nd September 2021.



**Keywords:** Advanced lung disease; Breathlessness; Chronic obstructive pulmonary disease; Community; Interstitial lung disease; Intervention; Music therapy; Online; Singing.



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## Conflict of interest statement

The authors declare that they have no competing interests.

- 56 references
- 1 figure

SUPPLEMENTARY INFO

Publication types, MeSH termsexpand

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Review

Cell Death Discov

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. 2022 Aug 16;8(1):363.

doi: 10.1038/s41420-022-01154-7.

# Role of necroptosis in airflow limitation in chronic obstructive pulmonary disease: focus on small-airway disease and emphysema

Chanjing Liu[1], Peijun Li[1], Jiejiao Zheng[2], Yingqi Wang[1], Weibing Wu[3], Xiaodan Liu[4]

Affiliations expand

- PMID: 35973987

- PMCID: PMC9381515

- DOI: 10.1038/s41420-022-01154-7

# Abstract

Airflow limitation with intractable progressive mechanisms is the main disease feature of chronic obstructive pulmonary disease (COPD). The pathological process of airflow limitation in COPD involves necroptosis, a form of programmed necrotic cell death with pro-inflammatory properties. In this paper, the correlations of small-airway disease and emphysema with airflow limitation in COPD were firstly reviewed; then, based on this, the effects of necroptosis on small-airway disease and emphysema were analysed, and the possible mechanisms of necroptosis causing airflow limitation in COPD were explored. The results showed that airflow limitation is caused by a combination of small-airway disease and emphysema. In addition, toxic particulate matter stimulates epithelial cells to trigger necroptosis, and necroptosis promotes the expulsion of cell contents, the abnormal hyperplasia of pro-inflammatory mediators and the insufficient clearance of dead cells by macrophages; these processes, coupled with the interaction of necroptosis and oxidative stress, collectively result in small-airway disease and emphysema in COPD.

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## Conflict of interest statement

The authors declare no competing interests.

- 51 references
- 3 figures

SUPPLEMENTARY INFO

Publication types, Grant supportexpand

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10

Meta-Analysis

PLoS One

. 2022 Aug 16;17(8):e0273042.

doi: 10.1371/journal.pone.0273042. eCollection 2022.

# Association of hypoxia inducible factor 1-Alpha gene polymorphisms with multiple disease risks: A comprehensive meta-analysis

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Affiliations expand

- PMID: 35972942

- PMCID: PMC9380912

- DOI: 10.1371/journal.pone.0273042

## Abstract

HIF1A gene polymorphisms have been confirmed the association with cancer risk through the statistical meta-analysis based on single genetic association (SGA) studies. A good number SGA studies also investigated the association of HIF1A gene with several other diseases, but no researcher yet performed statistical meta-analysis to confirm this association more accurately. Therefore, in this paper, we performed a statistical meta-analysis to draw a consensus decision about the association of HIF1A gene polymorphisms with several diseases except cancers giving the weight on large sample size. This meta-analysis was performed based on 41 SGA study's findings, where the polymorphisms rs11549465 (1772 C/T) and rs11549467 (1790 G/A) of HIF1A gene were analyzed based on 11544 and 7426 cases and 11494 and 7063 control samples, respectively. Our results showed that the 1772 C/T polymorphism is not significantly associated with overall disease risks. The 1790 G/A polymorphism was significantly associated with overall diseases under recessive model (AA vs. AG + GG), which indicates that the A allele is responsible for overall diseases though it is recessive. The subgroup analysis based on ethnicity showed the significant association of 1772 C/T polymorphism with overall disease for Caucasian population under the all genetic models, which indicates that the C allele controls overall diseases. The ethnicity subgroup showed the significant association of 1790 G/A

polymorphism with overall disease for Asian population under the recessive model (AA vs. AG + GG), which indicates that the A allele is responsible for overall diseases. The subgroup analysis based on disease types showed that 1772 C/T is significantly associated with chronic obstructive pulmonary disease (COPD) under two genetic models (C vs. T and CC vs. CT + TT), skin disease under two genetic models (CC vs. TT and CC + CT vs. TT), and diabetic complications under three genetic models (C vs. T, CT vs. TT and CC + CT vs. TT), where C allele is high risk factor for skin disease and diabetic complications (since, ORs > 1), but low risk factor for COPD (since, ORs < 1). Also the 1790 G/A variant significantly associated with the subgroup of cardiovascular disease (CVD) under homozygote model, diabetic complications under allelic and homozygote models, and other disease under four genetic models, where the A is high risk factor for diabetic complications and low risk factor for CVD. Thus, this study provided more evidence that the HIF1A gene is significantly associated with COPD, CVD, skin disease and diabetic complications. These might be the severe comorbidities and risk factors for multiple cancers due to the effect of HIF1A gene and need further investigations accumulating large number of studies.

## Conflict of interest statement

The authors have declared that no competing interests exist.

- 89 references
- 4 figures

SUPPLEMENTARY INFO

Publication types, MeSH terms, Substances, Grant supportexpand

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Multicenter Study

Respir Res

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. 2022 Aug 15;23(1):207.

doi: 10.1186/s12931-022-02128-0.

# Impact of chronic obstructive pulmonary disease on short-term outcome in patients with ST-elevation myocardial infarction during COVID-19 pandemic: insights from the international multicenter ISACS-STEMI registry

Giuseppe De Luca[1,2], Matteo Nardin[3], Magdy Algowhary[4], Berat Uguz[5], Dinaldo C Oliveira[6], Vladimir Ganyukov[7], Zan Zimbakov[8], Miha Cercek[9], Lisette Okkels Jensen[10], Poay Huan Loh[11], Lucian Calmac[12], Gerard Roura Ferrer[13], Alexandre Quadros[14], Marek Milewski[15], Fortunato Scotto di Uccio[16], Clemens von Birgelen[17], Francesco Versaci[18], Jurrien Ten Berg[19], Gianni Casella[20], Aaron Wong Sung Lung[21], Petr Kala[22], José Luis Díez Gil[23], Xavier Carrillo[24], Maurits Dirksen[25], Victor M Becerra-Munoz[26], Michael Kang-Yin Lee[27], Dafsah Arifa Juzar[28], Rodrigo de Moura Joaquim[29], Roberto Paladino[30], Davor Milicic[31], Periklis Davlouros[32], Nikola Bakraceski[33], Filippo Zilio[34], Luca Donazzan[35], Adriaan Kraaijeveld[36], Gennaro Galasso[37], Arpad Lux[38], Lucia Marinucci[39], Vincenzo Guiducci[40], Maurizio Menichelli[41], Alessandra Scoccia[42], Aylin Hatice Yamac[43], Kadir Ugur Mert[44], Xacobe Flores Rios[45], Tomas Kovarnik[46], Michal Kidawa[47], Josè Moreu[48], Vincent Flavien[49], Enrico Fabris[50], Iñigo Lozano Martínez-Luengas[51], Marco Boccalatte[52], Francisco Bosa Ojeda[53], Carlos Arellano-Serrano[54], Gianluca Caiazzo[55], Giuseppe Cirrincione[56], Hsien-Li Kao[57], Juan Sanchis Forés[58], Luigi Vignali[59], Helder Pereira[60], Stephane Manzo[61], Santiago Ordoñez[62], Alev Arat Özkan[63], Bruno Scheller[64], Heidi Lehtola[65], Rui Teles[66], Christos Mantis[67], Ylitalo Antti[68], João A Brum Silveira[69], Rodrigo Zoni[70], Ivan Bessonov[71], Stefano Savonitto[72], George Kochiadakis[73], Dimitrios Alexopoulos[74], Carlos E Uribe[75], John Kanakakis[76], Benjamin Faurie[77], Gabriele Gabrielli[78], Alejandro Gutierrez Barrios[79], Juan Pablo Bachini[80], Alex Rocha[81], Frankie Chor-Cheung Tam[82], Alfredo Rodriguez[83], Antonia Anna Lukito[84], Veauthyelau Saint-Joy[85], Gustavo Pessah[86], Andrea Tuccillo[16], Giuliana Cortese[87], Guido Parodi[88], Mohamed Abed Bouraghda[89], Elvin Kedhi[90], Pablo Lamelas[62], Harry Suryapranata[91], Monica Verdoia[92]

Affiliations expand

- PMID: 35971173

- PMCID: PMC9376902

- DOI: 10.1186/s12931-022-02128-0

# Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is projected to become the third cause of mortality worldwide. COPD shares several pathophysiological mechanisms with cardiovascular disease, especially atherosclerosis. However, no definite answers are available on the prognostic role of COPD in the setting of ST elevation myocardial infarction (STEMI), especially during COVID-19 pandemic, among patients undergoing primary angioplasty, that is therefore the aim of the current study.

**Methods:** In the ISACS-STEMI COVID-19 registry we included retrospectively patients with STEMI treated with primary percutaneous coronary intervention (PCI) between March and June of 2019 and 2020 from 109 high-volume primary PCI centers in 4 continents.

**Results:** A total of 15,686 patients were included in this analysis. Of them, 810 (5.2%) subjects had a COPD diagnosis. They were more often elderly and with a more pronounced cardiovascular risk profile. No preminent procedural dissimilarities were noticed except for a lower proportion of dual antiplatelet therapy at discharge among COPD patients (98.9% vs. 98.1%, P = 0.038). With regards to short-term fatal outcomes, both in-hospital and 30-days mortality occurred more frequently among COPD patients, similarly in pre-COVID-19 and COVID-19 era. However, after adjustment for main baseline differences, COPD did not result as independent predictor for in-hospital death (adjusted OR [95% CI] = 0.913[0.658-1.266], P = 0.585) nor for 30-days mortality (adjusted OR [95% CI] = 0.850 [0.620-1.164], P = 0.310). No significant differences were detected in terms of SARS-CoV-2 positivity between the two groups.

**Conclusion:** This is one of the largest studies investigating characteristics and outcome of COPD patients with STEMI undergoing primary angioplasty, especially during COVID pandemic. COPD was associated with significantly higher rates of in-hospital and 30-days mortality. However, this association disappeared after adjustment for baseline characteristics. Furthermore, COPD did not significantly affect SARS-CoV-2 positivity.

**Trial registration number:** NCT04412655 (2nd June 2020).

**Keywords:** COPD; Mortality; STEMI.

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## Conflict of interest statement

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

- 40 references

- 3 figures

SUPPLEMENTARY INFO

Publication types, MeSH terms, Associated dataexpand

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12

Sci Rep

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. 2022 Aug 15;12(1):13820.

doi: 10.1038/s41598-022-15612-w.

# FVC, but not FEV 1, is associated with clinical outcomes of asthma-COPD overlap

Tai Joon An [1], Chin Kook Rhee [2], Yong Bum Park [3], Kwang-Ha Yoo [4], Hyoung Kyu Yoon [5]

Affiliations expand

- PMID: 35970932

- PMCID: PMC9378661

- DOI: 10.1038/s41598-022-15612-w

## Abstract

The effects of forced vital capacity (FVC) on clinical outcomes of asthma-chronic obstructive pulmonary diseases overlap (ACO) are still unknown. We conducted this study

to examine the association of FVC on clinical outcomes in ACO. Data from the Korean COPD Subgroup Study cohort were analyzed. Patients who fulfilled the ACO criteria were included and grouped according to FVC changes, such as FVC-incline and FVC-decline. No significant differences were observed between the FVC-incline and FVC-decline groups in baseline clinical characteristics. In a year after, FVC-decline group experienced more moderate (47.1% vs. 36.8%, p = 0.02) and moderate-to-severe (49.8% vs. 39.6%, p = 0.03) acute exacerbations (AEs), compared to FVC-incline group. The frequency of moderate AEs (1.3 ± 2.1 vs. 0.9 ± 1.7, p = 0.03) and moderate-to-severe AEs (1.5 ± 2.5 vs. 1.1 ± 1.9, p = 0.04) were higher in the FVC-decline group than in the FVC-incline groups. After adjusting for confounding factors, FVC-decline group was associated with moderate AEs (odds ratio [OR] = 1.58; 95% confidence interval [CI] 1.02-2.44; p = 0.04), and moderate-to-severe AEs (OR = 1.56; 95% CI 1.01-2.41; p < 0.05) in ACO patients, which was not seen in $FEV_1$ changes. FVC changes are associated with clinical outcomes in ACO.

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## Conflict of interest statement

The authors declare no competing interests.

- 32 references
- 3 figures

SUPPLEMENTARY INFO

MeSH terms, Grant supportexpand

Proceed to details

Cite

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13

Respirology

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. 2022 Aug 15.

doi: 10.1111/resp.14339. Online ahead of print.

# Effect of chronic mucus hypersecretion on treatment responses to inhaled therapies in patients with chronic obstructive pulmonary disease: Post hoc analysis of the IMPACT trial

Philip J Thompson[1], Gerard J Criner[2], Mark T Dransfield[3], David M G Halpin[4], MeiLan K Han[5], David A Lipson[6,7], Ghassan J Maghzal[8], Fernando J Martinez[9], Dawn Midwinter[10], Dave Singh[11], Lee Tombs[12], Robert A Wise[13]

Affiliations expand

- PMID: 35970518

- DOI: 10.1111/resp.14339

## Abstract

**Background and objective:** Chronic mucus hypersecretion (CMH) is a clinical phenotype of COPD. This exploratory post hoc analysis assessed relationship between CMH status and treatment response in IMPACT.

**Methods:** Patients were randomized to once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 µg, FF/VI 100/25 µg or UMEC/VI 62.5/25 µg and designated CMH+ if they scored 1/2 in St George's Respiratory Questionnaire (SGRQ) questions 1 and 2. Endpoints assessed by baseline CMH status included on-treatment exacerbation rates, change from baseline in trough forced expiratory volume in 1 second, SGRQ total score, COPD Assessment Test (CAT) score, proportion of SGRQ and CAT responders at Week 52 and safety.

**Results:** Of 10,355 patients in the intent-to-treat population, 10,250 reported baseline SGRQ data (CMH+: 62% [n = 6383]). FF/UMEC/VI significantly ($p < 0.001$) reduced on-treatment moderate/severe exacerbation rates versus FF/VI and UMEC/VI in CMH+ (rate ratio: 0.87 and 0.72) and CMH- patients (0.82 and 0.80). FF/UMEC/VI significantly ($p < 0.05$) reduced on-treatment severe exacerbation rates versus UMEC/VI in CMH+ (0.62) and CMH- (0.74) subgroups. Similar improvements in health status and lung function with FF/UMEC/VI were observed, regardless of CMH status. In CMH+ patients, FF/VI significantly ($p < 0.001$) reduced on-treatment moderate/severe and severe exacerbation rates versus UMEC/VI (0.83 and 0.70).

**Conclusion:** FF/UMEC/VI had a favourable benefit: risk profile versus dual therapies irrespective of CMH status. The presence of CMH did not influence treatment response or exacerbations, lung function and/or health status. However, CMH did generate differences when dual therapies were compared and the impact of CMH should be considered in future trial design.

**Keywords:** COPD; chronic mucus hypersecretion; chronic obstructive pulmonary disease; clinical outcomes; single-inhaler triple therapy.

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- 29 references

SUPPLEMENTARY INFO

Grant supportexpand

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14

Clinical Trial

PLoS One

. 2022 Aug 15;17(8):e0273170.

doi: 10.1371/journal.pone.0273170. eCollection 2022.

# Correct use and ease-of-use of placebo ELLIPTA dry-powder inhaler in adult patients with chronic obstructive pulmonary disease

Thomas M Siler[1], Renu Jain[2], Kathryn Collison[2], Raj Sharma[3], Laura Sutton[2], Jamie Rees[4], David I Bernstein[5]

Affiliations expand

- PMID: 35969632

- PMCID: PMC9377593

- DOI: 10.1371/journal.pone.0273170

# Abstract

**Background:** Inhaler technique errors are common in chronic obstructive pulmonary disease (COPD) treatment, potentially leading to poor disease management. Our pooled analysis approach assessed correct use and ease-of-use of a placebo ELLIPTA dry-powder inhaler (DPI) in patients with COPD.

**Methods:** Adults with COPD from open-label/non-blinded studies evaluating a placebo ELLIPTA DPI and reporting outcomes of correct use (based on the ELLIPTA DPI patient information leaflet [PIL]) and/or ease-of-use were included. Correct use and ease-of use at study end were primary and secondary endpoints, respectively. Data from patients in the placebo ELLIPTA DPI arm of each study were pooled, and the intent-to-treat (ITT) population was used for all analyses.

**Results:** Four placebo ELLIPTA DPI studies, reporting correct use (n = 4) and ease-of-use (n = 2), were included in the analysis. The ITT population comprised 1232 patients (mean age 66.2 years). For the primary endpoint, 80.1% (n = 975/1217) of patients demonstrated correct use at study end (95% confidence interval [CI]: 77.8%-82.3%). For the secondary endpoint, 95.7% (n = 797/833) of patients rated placebo ELLIPTA DPI use "easy"/"very easy" at study end (95% CI: 94.1%-97.0%). Correct use and "easy"/"very easy" user ratings remained high across younger (40-64 years) and older (≥65 years) age groups.

**Conclusions:** Across age groups, most patients used the placebo ELLIPTA DPI correctly and rated it "easy"/"very easy" to use. Consistent with the Global Initiative for Chronic Obstructive Lung Disease 2021 report, our findings emphasize that proper training and clear instructions on PILs are important for optimal inhaler use.

## Conflict of interest statement

RJ, KC, RS, LS, and JR report employment with, and stock/share ownership in, GSK during study conduct. KC is currently employed by AstraZeneca and LS is no longer employed by

GSK. TMS received research support from West-Ward Pharmaceuticals, Theravance Biopharma US, Inc., GSK, Pearl Therapeutics, Chiesi, AstraZeneca, Novartis, Boehringer Ingelheim, Forest, Compleware, Evidera, Oncocyte, Teva, Vapotherm, Sunovion, Proterix BioPharma, Seer, and Sanofi. TMS has also received speaker fees from GSK, Mylan Inc./Theravance Biopharma US, Inc., and Sunovion, and consulting fees from Vapotherm. DIB received grant/research/clinical trial support from GSK, Teva, AstraZeneca, Pearl Therapeutics, Novartis, Genentech, Inc., Merck, Boehringer Ingelheim, Amgen, Aimmune, Shire, and Biocryst and consulted/participated in advisory boards for GSK, ALK America, Gerson-Lehman, and Guidepoint Global. This does not alter our adherence to PLOS ONE policies on sharing data and materials.


- 33 references
- 4 figures

SUPPLEMENTARY INFO

Publication types, MeSH terms, Substances, Grant supportexpand

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Ann Am Thorac Soc

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. 2022 Aug 15.

doi: 10.1513/AnnalsATS.202203-226OC. Online ahead of print.


# Diffusing Capacity and Mortality in Chronic Obstructive Pulmonary Disease


Aparna Balasubramanian[1], Nirupama Putcha[2,3], Neil R MacIntyre[4], Robert L Jensen[5], Gregory Kinney[6,7], William W Stringer[8], Craig P Hersh[9], Russell P Bowler[10], Richard Casaburi[11], MeiLan K Han[12], Janos Porszasz[8], R Graham Barr[13], Elizabeth Regan[14], Barry J Make[15], Nadia N Hansel[16], Robert A Wise[17], Meredith C McCormack[18]

Affiliations expand



- PMID: 35969416

- DOI: 10.1513/AnnalsATS.202203-226OC

# Abstract

**Rationale**: Chronic Obstructive Pulmonary Disease (COPD) mortality risk is often estimated using the BODE index (including body mass index, forced expiratory volume in one second (FEV1), dyspnea score, and six-minute walk distance). Diffusing capacity (DLCO) is a potential predictor of mortality that reflects physiology distinct from that in the BODE index. **Objectives**: This study evaluated DLCO as a predictor of mortality using participants from the COPDGene study. **Methods**: We performed time-to-event analyses of individuals with COPD (former/current smokers with FEV1/FVC <0.7) and DLCO measurements from the COPDGene Phase 2 visit. Cox proportional hazard methods were used to model survival, adjusting for age, sex, pack-years, smoking status, BODE index, computed tomography (CT) percent emphysema (low attenuation areas <-950 Hounsfield units), CT airway wall thickness, and history of cardiovascular or kidney diseases. C-statistics for models with DLCO and BODE score were used to compare discriminative accuracy. **Results**: Of 2329 participants, 378(16.8%) died during the follow-up period (median 4.9 years). In adjusted analyses, for every 10% decrease in DLCO %predicted, mortality increased by 29% (Hazard ratio 1.29, 95% CI 1.17 - 1.41, p<0.001). When compared to other clinical predictors, DLCO %predicted performed similarly to BODE (C-statistic DLCO 0.68, BODE 0.70), and the addition of DLCO to BODE improved its discriminative accuracy (C-statistic 0.71). **Conclusions**: Diffusing capacity, a measure of gas transfer, strongly predicted all-cause mortality in individuals with COPD, independent of BODE index and CT evidence of emphysema and airway wall thickness. These findings support inclusion of DLCO in prognostic models for COPD.

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Am J Respir Crit Care Med

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. 2022 Aug 15;206(4):e7-e41.

doi: 10.1164/rccm.202206-1041ST.

# Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement

Vincent Cottin, Moises Selman, Yoshikazu Inoue, Alyson W Wong, Tamera J Corte, Kevin R Flaherty, MeiLan K Han, Joseph Jacob, Kerri A Johannson, Masanori Kitaichi, Joyce S Lee, Alvar Agusti, Katerina M Antoniou, Pauline Bianchi, Fabian Caro, Matias Florenzano, Liam Galvin, Tae Iwasawa, Fernando J Martinez, Rebecca L Morgan, Jeffrey L Myers, Andrew G Nicholson, Mariaelena Occhipinti, Venerino Poletti, Margaret L Salisbury, Don D Sin, Nicola Sverzellati, Thomy Tonia, Claudia Valenzuela, Christopher J Ryerson, Athol U Wells

- PMID: 35969190

- DOI: 10.1164/rccm.202206-1041ST

## Abstract

**Background:** The presence of emphysema is relatively common in patients with fibrotic interstitial lung disease. This has been designated combined pulmonary fibrosis and emphysema (CPFE). The lack of consensus over definitions and diagnostic criteria has limited CPFE research. **Goals:** The objectives of this task force were to review the terminology, definition, characteristics, pathophysiology, and research priorities of CPFE and to explore whether CPFE is a syndrome. **Methods:** This research statement was developed by a committee including 19 pulmonologists, 5 radiologists, 3 pathologists, 2 methodologists, and 2 patient representatives. The final document was supported by a focused systematic review that identified and summarized all recent publications related to CPFE. **Results:** This task force identified that patients with CPFE are predominantly male, with a history of smoking, severe dyspnea, relatively preserved airflow rates and lung volumes on spirometry, severely impaired $DI_{CO}$, exertional hypoxemia, frequent pulmonary hypertension, and a dismal prognosis. The committee proposes to identify CPFE as a syndrome, given the clustering of pulmonary fibrosis and emphysema, shared pathogenetic pathways, unique considerations related to disease progression, increased risk of complications (pulmonary hypertension, lung cancer, and/or mortality), and implications for clinical trial design. There are varying features of interstitial lung disease and emphysema in CPFE. The committee offers a research definition and classification criteria and proposes that studies on CPFE include a comprehensive description of radiologic and, when available, pathological patterns, including some recently described patterns such as smoking-related interstitial fibrosis. **Conclusions:** This statement delineates the syndrome of CPFE and highlights research priorities.

**Keywords:** diagnosis; emphysema; fibrosis; interstitial lung disease; management.

SUPPLEMENTARY INFO

MeSH termsexpand

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Review

Toxicol Appl Pharmacol

. 2022 Aug 15;449:116070.

doi: 10.1016/j.taap.2022.116070. Epub 2022 May 23.

# Inflammation resolution in environmental pulmonary health and morbidity

Jacqui M Marzec[1], Srikanth S Nadadur[2]

Affiliations expand

- PMID: 35618031

- DOI: 10.1016/j.taap.2022.116070

## Abstract

Inflammation and resolution are dynamic processes comprised of inflammatory activation and neutrophil influx, followed by mediator catabolism and efferocytosis. These critical pathways ensure a return to homeostasis and promote repair. Over the past decade

research has shown that diverse mediators play a role in the active process of resolution. Specialized pro-resolving mediators (SPMs), biosynthesized from fatty acids, are released during inflammation to facilitate resolution and are deficient in a variety of lung disorders. Failed resolution results in remodeling and cellular deposition through pro-fibrotic myofibroblast expansion that irreversibly narrows the airways and worsens lung function. Recent studies indicate environmental exposures may perturb and deregulate critical resolution pathways. Environmental xenobiotics induce lung inflammation and generate reactive metabolites that promote oxidative stress, injuring the respiratory mucosa and impairing gas-exchange. This warrants recognition of xenobiotic associated molecular patterns (XAMPs) as new signals in the field of inflammation biology, as many environmental chemicals generate free radicals capable of initiating the inflammatory response. Recent studies suggest that unresolved, persistent inflammation impacts both resolution pathways and endogenous regulatory mediators, compromising lung function, which over time can progress to chronic lung disease. Chronic ozone ($O_3$) exposure overwhelms successful resolution, and in susceptible individuals promotes asthma onset. The industrial contaminant cadmium (Cd) bioaccumulates in the lung to impair resolution, and recurrent inflammation can result in chronic obstructive pulmonary disease (COPD). Persistent particulate matter (PM) exposure increases systemic cardiopulmonary inflammation, which reduces lung function and can exacerbate asthma, COPD, and idiopathic pulmonary fibrosis (IPF). While recurrent inflammation underlies environmentally induced pulmonary morbidity and may drive the disease process, our understanding of inflammation resolution in this context is limited. This review aims to explore inflammation resolution biology and its role in chronic environmental lung disease(s).

**Keywords:** ALI; Asthma; COPD; Clearance; Environment; Gasotransmitters; IPF; Inflammation; Oxidative stress; Pollutants; Resolution; SPMs.

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- Cited by 1 article

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Am J Respir Crit Care Med

. 2022 Aug 15;206(4):516-517.

doi: 10.1164/rccm.202202-0350LE.

# Small Airways in Pulmonary Fibrosis: Revisiting an Old Question with New Tools

Vincent Cottin[1,2]

Affiliations expand

- PMID: 35549841

- DOI: 10.1164/rccm.202202-0350LE

*No abstract available*

SUPPLEMENTARY INFO

Publication types, MeSH termsexpand

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Am J Respir Crit Care Med

. 2022 Aug 15;206(4):427-439.

doi: 10.1164/rccm.202110-2241OC.

# Lung Microbiota and Metabolites Collectively Associate with Clinical Outcomes in Milder Stage Chronic Obstructive Pulmonary Disease

Siddharth S Madapoosi[1], Charmion Cruickshank-Quinn[2], Kristopher Opron[1], John R Erb-Downward[1], Lesa A Begley[1], Gen Li[3], Igor Barjaktarevic[4], R Graham Barr[5,6], Alejandro P Comellas[7], David J Couper[8], Christopher B Cooper[4], Christine M Freeman[1], MeiLan K Han[1], Robert J Kaner[9], Wassim Labaki[1], Fernando J Martinez[9], Victor E Ortega[10], Stephen P Peters[10], Robert Paine[11], Prescott Woodruff[12], Jeffrey L Curtis[1,13], Gary B Huffnagle[1,14], Kathleen A Stringer[15], Russell P Bowler[16,17], Charles R Esther Jr[18,19], Nichole Reisdorph[2], Yvonne J Huang[1,20], SPIROMICS Research Group

Collaborators, Affiliations expand

- PMID: 35536732

- DOI: 10.1164/rccm.202110-2241OC

## Abstract

**Rationale:** Chronic obstructive pulmonary disease (COPD) is variable in its development. Lung microbiota and metabolites collectively may impact COPD pathophysiology, but relationships to clinical outcomes in milder disease are unclear. **Objectives:** Identify components of the lung microbiome and metabolome collectively associated with clinical markers in milder stage COPD. **Methods:** We analyzed paired microbiome and metabolomic data previously characterized from bronchoalveolar lavage fluid in 137 participants in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study), or (GOLD [Global Initiative for Chronic Obstructive Lung Disease Stage 0-2). Datasets used included *1*) bacterial 16S rRNA gene sequencing; *2*) untargeted metabolomics of the hydrophobic fraction, largely comprising lipids; and *3*) targeted metabolomics for a panel of hydrophilic compounds previously implicated in mucoinflammation. We applied an integrative approach to select features and model 14 individual clinical variables representative of known associations with COPD trajectory (lung function, symptoms, and exacerbations). **Measurements and Main Results:** The

majority of clinical measures associated with the lung microbiome and metabolome collectively in overall models (classification accuracies, >50%, $P < 0.05$ vs. chance). Lower lung function, COPD diagnosis, and greater symptoms associated positively with *Streptococcus*, *Neisseria*, and *Veillonella*, together with compounds from several classes (glycosphingolipids, glycerophospholipids, polyamines and xanthine, an adenosine metabolite). In contrast, several *Prevotella* members, together with adenosine, 5'-methylthioadenosine, sialic acid, tyrosine, and glutathione, associated with better lung function, absence of COPD, or less symptoms. Significant correlations were observed between specific metabolites and bacteria ($P_{adj} < 0.05$). **Conclusions:** Components of the lung microbiome and metabolome in combination relate to outcome measures in milder COPD, highlighting their potential collaborative roles in disease pathogenesis.

**Keywords:** bronchoscopy; chronic obstructive pulmonary disease; lung function; metabolomics.

## Comment in

- Microbiomics-focused Data Integration: A Fresh Solve for the Rubik's Cube of Endophenotyping?
  Narayana JK, Tsaneva-Atanasova K, Chotirmall SH.Am J Respir Crit Care Med. 2022 Aug 15;206(4):365-368. doi: 10.1164/rccm.202205-0860ED.PMID: 35584334 No abstract available.

SUPPLEMENTARY INFO

MeSH terms, Substances, Grant supportexpand

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doi: 10.1164/rccm.202108-1943OC.

# Endotyping Chronic Obstructive Pulmonary Disease, Bronchiectasis, and the "Chronic Obstructive Pulmonary Disease–Bronchiectasis Association"

Jeffrey T-J Huang[1], Erin Cant[2], Holly R Keir[2], Alun K Barton[1], Elena Kuzmanova[1], Morven Shuttleworth[2], Jennifer Pollock[2], Simon Finch[2], Eva Polverino[3], Mathieu Bottier[2], Alison J Dicker[1], Amelia Shoemark[2], James D Chalmers[2]

Affiliations expand

- PMID: 35436182

- DOI: 10.1164/rccm.202108-1943OC

## Abstract

**Rationale:** Bronchiectasis and chronic obstructive pulmonary disease (COPD) are two disease entities with overlapped clinical features, and codiagnosis frequently occurs (termed the "COPD-bronchiectasis association"). **Objectives:** To investigate the sputum microbiome and proteome in patients with bronchiectasis, COPD, and the COPD-bronchiectasis association with the aim of identifying endotypes that may inform treatment. **Methods:** Sputum microbiome and protein profiling were carried out using 16S rRNA amplicon sequencing and a label-free proteomics workflow, respectively, in a cohort comprising patients with COPD (*n* = 43), bronchiectasis (*n* = 30), and the COPD-bronchiectasis association (*n* = 48). Results were validated in an independent cohort of 91 patients (*n* = 28-31 each group) using targeted measurements of inflammatory markers, mucins, and bacterial culture. **Measurements and Main Results:** Principal component analysis of sputum microbiome and protein profiles showed a partial separation between the COPD and the "COPD-bronchiectasis association" group. Further analyses revealed that patients with the "COPD-bronchiectasis association" had a higher abundance of proteobacteria, higher expression of mucin-5AC and proteins from the "neutrophil degranulation" pathway compared to those with COPD. In contrast, patients with COPD had an elevated expression of mucin-5B and several peptidase inhibitors, higher abundance of common commensal taxa, and a greater microbiome diversity. The profiles of "COPD-bronchiectasis association" and bronchiectasis groups were largely overlapping.

Five endotypes were proposed with differential inflammatory, mucin, and microbiological features. The key features related to the "COPD-bronchiectasis association" were validated in an independent cohort. **Conclusions:** Neutrophilic inflammation, differential mucin expression, and Gram-negative infection are dominant traits in patients with the "COPD-bronchiectasis association."

**Keywords:** COPD; bronchiectasis; endotype; microbiome; proteome; sputum; the “COPD–bronchiectasis association”.

## Comment in

- Microbiomics-focused Data Integration: A Fresh Solve for the Rubik's Cube of Endophenotyping?
  Narayana JK, Tsaneva-Atanasova K, Chotirmall SH.Am J Respir Crit Care Med. 2022 Aug 15;206(4):365-368. doi: 10.1164/rccm.202205-0860ED.PMID: 35584334 No abstract available.

SUPPLEMENTARY INFO

MeSH terms, Substances, Grant supportexpand

FULL TEXT LINKS

AJRCCM Full Text

## ASTHMA

1

Environ Res

. 2022 Aug 18;114116.

doi: 10.1016/j.envres.2022.114116. Online ahead of print.

# Asthma mortality attributable to ambient temperatures: A case-crossover study in China

Yun Zhou[1], Jingju Pan[2], Ruijun Xu[3], Wenfeng Lu[1], Yaqi Wang[3], Tingting Liu[3], Zhaoyu Fan[3], Yingxin Li[3], Chunxiang Shi[4], Lan Zhang[2], Yuewei Liu[5], Hong Sun[6]

Affiliations expand

- PMID: 35988831

- DOI: 10.1016/j.envres.2022.114116

## Abstract

**Background:** Whether ambient temperature exposure contributes to death from asthma remains unknown to date. We therefore conducted a case-crossover study in China to quantitatively evaluate the association and burden of ambient temperature exposure on asthma mortality.

**Methods:** Using data from the National Mortality Surveillance System in China, we conducted a time-stratified case-crossover study of 15 888 individuals who lived in Hubei and Jiangsu province, China and died from asthma as the underlying cause in 2015-2019. Individual-level exposures to air temperature and apparent temperature on the date of death and 21 days prior were assessed based on each subject's residential address. Distributed lag nonlinear models based on conditional logistic regression were used to quantify exposure-response associations and calculate fraction and number of deaths attributable to non-optimum ambient temperatures.

**Results:** We observed a reverse J-shaped association between air temperature and risk of asthma mortality, with a minimum mortality temperature of 21.3 °C. Non-optimum ambient temperature is responsible for substantial excess mortality from asthma. In total, 26.3% of asthma mortality were attributable to non-optimum temperatures, with moderate cold, moderate hot, extreme cold and extreme hot responsible for 21.7%, 2.4%, 2.1% and 0.9% of asthma mortality, respectively. The total attributable fraction and number was significantly higher among adults aged less than 80 years in hot temperature.

**Conclusions:** Exposure to non-optimum ambient temperature, especially moderate cold temperature, was responsible for substantial excess mortality from asthma. These findings have important implications for planning of public-health interventions to minimize the adverse respiratory damage from non-optimum ambient temperature.

**Keywords:** Ambient temperatures; Asthma mortality; Case-crossover study; Exposure-response relationship; Non-optimum ambient temperature.

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## Conflict of interest statement

Declaration of competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Lancet Child Adolesc Health

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. 2022 Aug 18;S2352-4642(22)00185-7.

doi: 10.1016/S2352-4642(22)00185-7. Online ahead of print.

# Obesity-related asthma in children and adolescents

Jessica Reyes-Angel [1], Parisa Kaviany [2], Deepa Rastogi [2], Erick Forno [3]

Affiliations expand

- PMID: 35988550

- DOI: 10.1016/S2352-4642(22)00185-7

## Abstract

There is substantial epidemiological and experimental evidence of an obesity-related asthma phenotype. Compared to children of healthy weight, children with obesity are at higher risk of asthma. Children with obesity who have asthma have greater severity and poorer control of their asthma symptoms, more frequent asthma exacerbations, and overall lower asthma-related quality of life than children with asthma who have a healthy weight. In this Review, we examine some of the latest evidence on the characteristics of this phenotype and its main underlying mechanisms, including genetics and genomics, changes in airway mechanics and lung function, sex hormone differences, alterations in immune responses, systemic and airway inflammation, metabolic dysregulation, and modifications in the microbiome. We also review current recommendations for the treatment of these children, including in the management of their asthma, and current evidence for weight loss interventions. We then discuss initial evidence for potential novel therapeutic approaches, such as dietary modifications and supplements, antidiabetic medications, and statins. Finally, we identify knowledge gaps and future directions to improve our understanding of asthma in children with obesity, and to improve outcomes in these susceptible children. We highlight important needs, such as designing paediatric-specific studies, implementing large multicentric trials with standardised interventions and outcomes, and including racial and ethnic groups along with other under-represented populations that are particularly affected by obesity and asthma.

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## Conflict of interest statement

Declaration of interests We declare no competing interests.

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Publication typesexpand

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Review

Lancet Microbe

. 2022 Aug 18;S2666-5247(22)00184-7.

doi: 10.1016/S2666-5247(22)00184-7. Online ahead of print.

# The association between early-life gut microbiota and childhood respiratory diseases: a systematic review

Cristina Garcia-Maurino Alcazar[1], Veena Mazarello Paes[2], Yan Shao[3], Clarissa Oesser[4], Ada Miltz[4], Trevor D Lawley[3], Peter Brocklehurst[5], Alison Rodger[6], Nigel Field[4]

Affiliations expand

- PMID: 35988549

- DOI: 10.1016/S2666-5247(22)00184-7

## Abstract

Data from animal models suggest a role of early-life gut microbiota in lung immune development, and in establishing susceptibility to respiratory infections and asthma in humans. This systematic review summarises the association between infant (ages 0-12 months) gut microbiota composition measured by genomic sequencing, and childhood (ages 0-18 years) respiratory diseases (ie, respiratory infections, wheezing, or asthma). Overall, there was evidence that low α-diversity and relative abundance of particular gut-commensal bacteria genera (Bifidobacterium, Faecalibacterium, Ruminococcus, and Roseburia) are associated with childhood respiratory diseases. However, results were inconsistent and studies had important limitations, including insufficient characterisation of bacterial taxa to species level, heterogeneous outcome definitions, residual confounding, and small sample sizes. Large longitudinal studies with stool sampling during the first month of life and shotgun metagenomic approaches to improve bacterial and fungal taxa resolution are needed. Standardising follow-up times and respiratory disease definitions and optimising causal statistical approaches might identify targets for primary prevention of childhood respiratory diseases.

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### Conflict of interest statement

Declaration of interests We declare no competing interests.

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Publication typesexpand

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J Allergy Clin Immunol Pract

. 2022 Aug 17;S2213-2198(22)00817-0.

doi: 10.1016/j.jaip.2022.08.013. Online ahead of print.

# Safety of biologics for atopic diseases during pregnancy

Fnu Shakuntulla[1], Sergio E Chiarella[2]

Affiliations expand

- PMID: 35987486

- DOI: 10.1016/j.jaip.2022.08.013

## Abstract

The high prevalence of atopic diseases in women of childbearing age reveals the need to determine the safety of biologics during pregnancy. This review summarizes the effects of seven FDA-approved biologics (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and tralokinumab) on maternal and fetal outcomes. For this purpose, we reviewed English-language publications to investigate whether the use of biologics for atopic diseases during pregnancy increased the risk of preterm delivery, stillbirth, low birth weight, or congenital malformations. Most publications found were case reports, case series, or observational studies reporting outcomes in a total of 313 pregnancies. No randomized controlled studies were identified. We found that biologics do not seem to influence maternal or fetal outcomes. Indeed, worsening of the underlying

atopic disease during pregnancy appears to be more detrimental to the viability of the pregnancy. Given the small sample size and scarcity of studies, future research should include prospective studies with comparable control groups without exposure to biologics and multicenter registries for long-term follow-up.

**Keywords:** Atopic diseases; asthma; atopic dermatitis; benralizumab; biologics; birth weight; chronic urticaria; congenital malformations; dupilumab; mepolizumab; omalizumab; pregnancy; preterm; reslizumab; safety; stillbirth; tezepelumab; tralokinumab.

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Allergy

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. 2022 Aug 20.

doi: 10.1111/all.15487. Online ahead of print.

# IL1RAP expression and the enrichment of IL-33 activation signatures in severe neutrophilic asthma

Yusef Eamon Badi[1 2 3], Barbora Salcman[4], Adam Taylor[5], Batika Rana[6], Nazanin Zounemat Kermani[2], John H Riley[4], Sally Worsley[7], Sharon Mumby[1], Sven-Eric Dahlen[8], David Cousins[9], Silvia Bulfone-Paus[4], Karen Affleck[10], Kian Fan Chung[1], Stewart Bates[# 4], Ian M Adcock[# 1]

Affiliations expand

- PMID: 35986608

- DOI: 10.1111/all.15487

## Abstract

**Background:** Interleukin (IL) -33 is an upstream regulator of type 2 (T2) eosinophilic inflammation and has been proposed as a key driver of some asthma phenotypes.

**Objective:** To derive gene signatures from in vitro studies of IL-33-stimulated cells and use these to determine IL-33-associated enrichment patterns in asthma.

**Methods:** Signatures downstream of IL-33 stimulation were derived from our in vitro study of human mast cells and from public datasets of in vitro stimulated human basophils, type 2 innate lymphoid cells (ILC2), regulatory T-cells (Treg) and endothelial cells. Gene Set Variation Analysis (GSVA) was used to probe U-BIOPRED and ADEPT sputum transcriptomics to determine enrichment scores (ES) for each signature according to asthma severity, sputum granulocyte status and previously-defined molecular phenotypes.

**Results:** IL-33-activated gene signatures were cell-specific with little gene overlap. Individual signatures, however, were associated with similar signalling pathways (TNF, NF-κB, IL-17 and JAK/STAT signalling) and immune cell differentiation pathways (Th17, Th1 and Th2 differentiation). ES for IL-33-activated gene signatures were significantly enriched in asthmatic sputum, particularly in patients with neutrophilic and mixed granulocytic phenotypes. IL-33 mRNA expression was not elevated in asthma whereas the expression of mRNA for IL1RL1, the IL-33 receptor, was upregulated in the sputum of severe eosinophilic asthma. The mRNA expression for IL1RAP, the IL1RL1 co-receptor, was greatest in severe neutrophilic and mixed granulocytic asthma.

**Conclusions:** IL-33-activated gene signatures are elevated in neutrophilic and mixed granulocytic asthma corresponding with IL1RAP co-receptor expression. This suggests incorporating T2-low asthma in anti-IL-33 trials.

**Keywords:** IL-33; gene set variation analysis; severe asthma.

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Thorax

. 2022 Aug 19;thorax-2022-219388.

doi: 10.1136/thorax-2022-219388. Online ahead of print.

# From bronchiolitis endotyping to asthma risk assessment

Silvia Carraro[1], Valentina Agnese Ferraro[2], Stefania Zanconato[2]

Affiliations expand

- PMID: 35985818

- DOI: 10.1136/thorax-2022-219388

*No abstract available*

**Keywords:** Asthma; Paediatric Lung Disaese.

## Conflict of interest statement

Competing interests: SC and VAF have no conflict of interest to declare; SZ reports financial support from Sanofi outside this work.

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BMJ Open

. 2022 Aug 19;12(8):e058356.

doi: 10.1136/bmjopen-2021-058356.

# Preventing unscheduled hospitalisations from asthma: a retrospective cohort study using routine primary and secondary care

# data in the UK (The PUSH-Asthma Study)-protocol paper

Nikita Simms-Williams[1], Prasad Nagakumar[2,3], Rasiah Thayakaran[1], Nicola Adderley[1], Richard Hotham[1], Adel Mansur[3,4], Krishnarajah Nirantharakumar[1], Shamil Haroon[1]

Affiliations expand

- PMID: 35985783

- DOI: 10.1136/bmjopen-2021-058356

## Abstract

**Introduction:** Asthma is the most common chronic respiratory disease in children and adults. Asthma results in significant disease-related morbidity, healthcare costs and, in some cases, death. Despite efforts through implementation of national guidelines to improve asthma care, the UK has one of the highest asthma-related morbidity and mortality rates in the western world. New approaches are necessary to prevent asthma attacks in children and adults. The objectives of this study are to assess the association between demographic and clinical factors and asthma-related hospital admissions in children and adults, describe the epidemiology of asthma phenotypes among hospital attenders, and externally validate existing asthma risk prediction models.

**Methods and analysis:** This is a retrospective cohort study of children and adults with asthma. Data will be extracted from the Clinical Practice Research Datalink (CPRD) Aurum database, which holds anonymised primary care data for over 13 million actively registered patients and covers approximately 19% of the UK population. The primary outcome will be asthma-related hospital admissions. The secondary outcomes will be prescriptions of short courses of oral corticosteroids (as a surrogate measure for asthma exacerbations), a composite outcome measure including hospital admissions and prescriptions of short courses of oral corticosteroids and delivery of asthma care management following hospital discharge. The primary analysis will use a Poisson regression model to assess the association between demographic and clinical risk factors and the primary and secondary outcomes. Latent class analysis will be used to identify distinct subgroups, which will further our knowledge on potential phenotypes of asthma among patients at high risk of asthma-related hospital admissions. A Concordance statistic (C-statistic) and logistic regression model will also be used to externally validate existing risk prediction models for asthma-related hospitalisations to allow for the optimal model to be identified and evaluated provide evidence for potential use of the optimal performing risk prediction model in primary care.

**Ethics and dissemination:** This study was approved by the CPRD Independent Scientific Advisory Committee (reference number: 21_000512). Findings from this study will be published in a peer-reviewed journal and disseminated at national and international conferences.

**Keywords:** Asthma; EPIDEMIOLOGY; PUBLIC HEALTH; RESPIRATORY MEDICINE (see Thoracic Medicine).

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## Conflict of interest statement

Competing interests: None declared.

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Dermatol Ther (Heidelb)

. 2022 Aug 19.

doi: 10.1007/s13555-022-00791-1. Online ahead of print.

# Dupilumab Treatment of Atopic Dermatitis in Routine Clinical Care: Baseline Characteristics of Patients in the PROLEAD Prospective, Observational Study

Diamant Thaçi[1], Andrea Bauer[2], Ralph von Kiedrowski[3], Florian Schenck[4], Konstantin Ertner[5], Sophie Möller[6], Anja Fait[7], Mike Bastian[7], Matthias Augustin[8]

Affiliations expand

- PMID: 35984627

- DOI: 10.1007/s13555-022-00791-1

# Abstract

**Introduction:** Dupilumab is the first biologic licensed to treat patients with moderate-to-severe atopic dermatitis (AD) who require systemic therapy. PROLEAD was designed to document the real-world effectiveness and safety of dupilumab in patients with moderate-to-severe AD. The present study aims to describe the baseline characteristics of patients treated with dupilumab in Germany.

**Methods:** PROLEAD is a national, multicentre, prospective, non-interventional study, with a 2-year observation period. Adults with moderate-to-severe AD treated with dupilumab were included. Baseline characteristics, physician assessments, and patient-reported outcomes (PROs) were collected.

**Results:** The study involved 126 sites throughout Germany. Of 839 patients assessed for eligibility, 828 were included, with baseline data available for 817 patients. Mean (standard deviation, SD) age of patients was 43.4 (15.8) years, with 396 (48.5%) patients being female. Overall, 66.6% of patients received their first diagnosis of AD during childhood. In total, 423 (51.8%) patients had co-existing atopic and type 2 inflammatory diseases, including allergic conjunctivitis (36.8%) and bronchial asthma (22.5%). Overall, 61.4% of patients had received systemic therapy, most commonly oral corticosteroids (49.9%). Approximately half of patients (51.3%) had received UV/phototherapy prior to baseline. Treatment with moderate-potent (Class 2) or potent (Class 3) topical corticosteroids was the most common concomitant treatment at baseline. However, 50.4% of patients had not received concomitant AD treatment with dupilumab at baseline. The most reported reason for initiating dupilumab was "Topical therapy alone was not sufficient" (95.1%). Mean (SD) physician assessments: EASI: 22.9 (14.5); SCORAD: 63.3 (16.2); IGA: 3.3 (0.7). Mean (SD) PROs: DLQI: 13.9 (7.1); peak pruritus NRS: 7.4 (2.3).

**Conclusions:** Patients with moderate-to-severe AD present a long medical history, impaired quality of life, and high prevalence of co-existing type 2 inflammatory diseases. Dupilumab was used as a first-line systemic treatment in 38.6% of patients.

**Keywords:** Atopic dermatitis; Biologic; Dupliumab; Real-world evidence.

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- 29 references

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Ann Am Thorac Soc

.
. 2022 Aug 19.

doi: 10.1513/AnnalsATS.202203-251PS. Online ahead of print.

# Switching Biological Therapies in Adults with Severe Asthma: What Are the Dilemmas and Is It Worthwhile?

John Politis[1], Philip G Bardin[1,2]

Affiliations expand

- PMID: 35984426

- DOI: 10.1513/AnnalsATS.202203-251PS

*No abstract available*

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10

Cell Mol Immunol

.
. 2022 Aug 19.

doi: 10.1038/s41423-022-00907-9. Online ahead of print.

# The membrane-associated ubiquitin ligases MARCH2 and MARCH3 target IL-5 receptor alpha to negatively regulate eosinophilic airway inflammation

Lin-Wen Zeng[1], Lu Feng[1], Rui Liu[1], Heng Lin[1], Hong-Bing Shu[1], Shu Li[2]

Affiliations expand

- PMID: 35982175

- DOI: 10.1038/s41423-022-00907-9

## Abstract

Interleukin 5 (IL-5) plays crucial roles in type 2-high asthma by mediating eosinophil maturation, activation, chemotaxis and survival. Inhibition of IL-5 signaling is considered a strategy for asthma treatment. Here, we identified MARCH2 and MARCH3 as critical negative regulators of IL-5-triggered signaling. MARCH2 and MARCH3 associate with the IL-5 receptor α chain (IL-5Rα) and mediate its K27-linked polyubiquitination at K379 and K383, respectively, and its subsequent lysosomal degradation. Deficiency of MARCH2 or MARCH3 modestly increases the level of IL-5Rα and enhances IL-5-induced signaling, whereas double knockout of MARCH2/3 has a more dramatic effect. March2/3 double knockout markedly increases the proportions of eosinophils in the bone marrow and peripheral blood in mice. Double knockout of March2/3 aggravates ovalbumin (OVA)-induced eosinophilia and causes increased inflammatory cell infiltration, peribronchial mucus secretion and production of Th2 cytokines. Neutralization of Il-5 attenuates OVA-induced airway inflammation and the enhanced effects of March2/3 double deficiency. These findings suggest that MARCH2 and MARCH3 play redundant roles in targeting IL-5Rα for degradation and negatively regulating allergic airway inflammation.

**Keywords:** Airway inflammation; Eosinophil; IL-5Rα; MARCH2/3; Polyubiquitination.

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- 37 references

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Sci Rep

. 2022 Aug 18;12(1):14104.

doi: 10.1038/s41598-022-18443-x.

# HSP70 upregulation in nasal mucosa of symptomatic children with allergic rhinitis and potential risk of asthma development

Anna Fagotti[#1], Livia Lucentini[#2], Francesca Simoncelli[1], Gianandrea La Porta[1], Leonardo Brustenga[1], Ilaria Bizzarri[3], Silvia Trio[3], Chiara Isidori[3], Ines Di Rosa[1], Giuseppe Di Cara[3]

Affiliations expand

- PMID: 35982171

- PMCID: PMC9388484

- DOI: 10.1038/s41598-022-18443-x

## Abstract

Allergic rhinitis and asthma are the most common causes of chronic inflammation of the upper and lower airways in childhood. However, a nasal biomarker that can link to pulmonary inflammation is yet to be found. The present paper aims to investigate the possible role in inflammation of two inducible 70-kDa Heat Shock Proteins (HSP70) members, HSPA1A/B and HSPA6, in nasal mucosa cells of allergic children through their mRNA expression analysis, and their correlation to both spirometric and FeNO values. The

relationship between FeNO in lower airways and ΔCts of HSPA1A/B in nasal mucosa seems to be influenced by clinical symptoms regardless of age, sex, and sensitization patterns. Therefore, HSP70 expression, as well as FeNO levels, could have a predictive capability to identify lower airways inflammation and thus to recognize rhinitic children having a potential risk of asthma development.

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## Conflict of interest statement

The authors declare no competing interests.

- 50 references
- 6 figures

SUPPLEMENTARY INFO

Grant supportexpand

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12

Review

J Allergy Clin Immunol

. 2022 Aug 15;S0091-6749(22)00915-0.

doi: 10.1016/j.jaci.2022.06.023. Online ahead of print.

# The role of the CBM complex in allergic inflammation and disease

Stanley B DeVore[1], Gurjit K Khurana Hershey[2]

Affiliations expand

- PMID: 35981904

- DOI: 10.1016/j.jaci.2022.06.023


# Abstract


The caspase activation and recruitment domain-coiled-coil (CARD-CC) family of proteins-CARD9, CARD10, CARD11, and CARD14-is collectively expressed across nearly all tissues of the body and is a crucial mediator of immunologic signaling as part of the CARD-B-cell lymphoma/leukemia 10-mucosa-associated lymphoid tissue lymphoma translocation protein 1 (CBM) complex. Dysfunction or dysregulation of CBM proteins has been linked to numerous clinical manifestations known as "CBM-opathies." The CBM-opathy spectrum encompasses diseases ranging from mucocutaneous fungal infections and psoriasis to combined immunodeficiency and lymphoproliferative diseases; however, there is accumulating evidence that the CARD-CC family members also contribute to the pathogenesis and progression of allergic inflammation and allergic diseases. Here, we review the 4 CARD-CC paralogs, as well as B-cell lymphoma/leukemia 10 and mucosa-associated lymphoid tissue lymphoma translocation protein 1, and their individual and collective roles in the pathogenesis and progression of allergic inflammation and 4 major allergic diseases (allergic asthma, atopic dermatitis, food allergy, and allergic rhinitis).



**Keywords:** Allergy; BCL10; CARD; CARD10; CARD11; CARD14; CARD9; CBM-opathy; MALT1; allergic rhinitis; asthma; atopic dermatitis; food allergy.



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13

Eur Respir J

. 2022 Aug 18;2200543.

doi: 10.1183/13993003.00543-2022. Online ahead of print.

# Interactions between spirometry and oscillometry in patients with moderate to severe asthma

Rory Chan[1], Brian Lipworth[2]

Affiliations expand

- PMID: 35981746

- DOI: 10.1183/13993003.00543-2022

*No abstract available*

SUPPLEMENTARY INFO

Publication typesexpand

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14

Curr Opin Allergy Clin Immunol

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. 2022 Aug 17.

doi: 10.1097/ACI.0000000000000852. Online ahead of print.

# Is allergy immunotherapy-induced anaphylaxis still a real problem?

David I Bernstein[1], Karen Berendts[2]

Affiliations expand

- PMID: 35980016

- DOI: 10.1097/ACI.0000000000000852

# Abstract

**Purpose of review:** The current review describes the incidence and risk for anaphylaxis due to allergy injections.

**Recent findings:** The incidence of fatal anaphylaxis occurs with approximately one in 7.2 million injection visits. Severe anaphylaxis may occur once in every 160 000 visits. The major risk for fatal anaphylaxis is severe and uncontrolled asthma.

**Summary:** Understanding risk factors for anaphylaxis to allergy injections has led to clinic protocols aimed at preventing such events. The efficacy of these preventive measures remains to be determined in future studies.

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- 17 references

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15

Editorial

Respirology

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. 2022 Aug 17.

doi: 10.1111/resp.14346. Online ahead of print.

# The severe asthma–obesity conundrum: Consequences for exertional dyspnoea and exercise tolerance in men and women

J Alberto Neder[1], Denis E O'Donnell[1]

Affiliations expand

- PMID: 35977722

- DOI: 10.1111/resp.14346

*No abstract available*

**Keywords:** asthma; exercise and pulmonary rehabilitation; respiratory structure and function; ventilation.

- 42 references

SUPPLEMENTARY INFO

Publication typesexpand

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16

Cell Rep Med

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. 2022 Aug 16;3(8):100722.

doi: 10.1016/j.xcrm.2022.100722.

# Like mother, like child: The maternal microbiome impacts offspring asthma

Isabel Tarrant[1], B Brett Finlay[2]

Affiliations expand

- PMID: 35977469

- DOI: 10.1016/j.xcrm.2022.100722

## Abstract

The link between the maternal microbiome and offspring allergy is poorly defined. McCauley and colleagues now demonstrate that heritable bacteria are associated with infant asthma susceptibility and induce immunosuppression of allergic inflammation, suggesting significant implications for asthma-preventative interventions[1].

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### Conflict of interest statement

Declaration of interests The authors declare no competing interests.

SUPPLEMENTARY INFO

MeSH termsexpand

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17

Tuberc Respir Dis (Seoul)

. 2022 Aug 17.

doi: 10.4046/trd.2022.0097. Online ahead of print.

# Respiratory Reviews in Asthma 2022

Ji Hye Lee[1], Jin-Young Kim[1], Jae Sung Choi[1], Ju Ock Na[1]

Affiliations expand

- PMID: 35974425

- DOI: 10.4046/trd.2022.0097

## Abstract

Asthma is a chronic inflammatory disease of the airways characterized by varying and recurrent symptoms, reversible airway obstruction, and bronchospasm. In this paper reviews clinical important studies on asthma between March 2021 and February 2022.<br/> A study on the relationship between asthma and chronic rhinosinusitis, bronchiectasis, and hormone replacement therapy was published, and a journal on the usefulness of fractional exhaled nitric oxide for the prediction of severe acute exacerbation was also introduced. Studies on the effect of inhaler, one of the most important treatments for asthma, and studies to control severe asthma continued, and phase 2 and 3 studies of new biologics were also published. As the COVID-19 pandemic has been prolonged, many studies have explored the prevalence and mortality of COVID-19 infection in asthma patients.

**Keywords:** Asthma; Biologics; COVID-19; Fractional exhaled nitric oxide; Inhaler therapy.

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18

J Asthma

- 
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. 2022 Aug 16;1-3.

doi: 10.1080/02770903.2022.2114085. Online ahead of print.

# Autonomic nervous system alterations in patients with mild-to-moderate asthma: do not forget airflow obstruction! A lesson from COPD

Alberto Fantin[1], Vincenzo Patruno[1], Giulia Sartori[2], Ernesto Crisafulli[2]

Affiliations expand

- PMID: 35972058

- DOI: 10.1080/02770903.2022.2114085

*No abstract available*

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19

Allergy

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. 2022 Aug 16.

doi: 10.1111/all.15480. Online ahead of print.

# Serum exosome inflamma-miRs are surrogate biomarkers for asthma phenotype and severity

Sara Vázquez-Mera[1,2], Laura Martelo-Vidal[1,2], Pablo Miguéns-Suárez[1,2], Paula Saavedra-Nieves[3], Pilar Arias[1,2], Coral González-Fernández[4], Mar Mosteiro-Añón[5], María Dolores Corbacho-Abelaira[6], Marina Blanco-Aparicio[7], Paula Méndez-Brea[8], Francisco Javier Salgado[1,2], Juan José Nieto-Fontarigo[2], Francisco Javier González-Barcala[2,9,10,11]

Affiliations expand

- PMID: 35971848

- DOI: 10.1111/all.15480

# Abstract

**Background:** Asthma is a heterogeneous disease with several phenotypes, endotypes and severity degrees, in which different T cell subpopulations are involved. These cells express specific miRNAs (i.e., inflamma-miRs) that can be released to serum in exosomes after activation and be used as biomarkers of underlying inflammation. Thus, we aim to evaluate specific T cell miRNA signatures in serum exosomes from different subgroups of asthmatic patients.

**Methods:** Samples from healthy donors (N=30) and patients (N=119) with different asthma endotypes ($T2^{high}$ -Atopic/$T2^{high}$ -Non atopic/$T2^{low}$ ) and severity degrees (mild/MA and moderate-severe/MSA) were used. Demographic, clinical, haematological and biochemical characteristics were collected. Twelve miRNAs previously associated with different Th subsets were preselected and their levels in serum exosome samples were measured using RTqPCR.

**Results:** We detected five miRNAs with high confidence in serum exosomes: miR-16-5p, miR-21-5p, miR-126-3p, miR146a-5p, and miR-215-5p. All of them, except miR-16-5p were upregulated in MSA patients compared to MA. A logistic regression model including each of these miRNAs was created to discriminate both conditions, rendering a ROC curve AUC of 0.896 (0.830-0.961). miR-21-5p and miR-126-3p, both involved in Th1/Th2 differentiation, were specifically augmented in $T2^{high}$ -Atopic patients. Of note, all these changes were found in samples collected in autumn. On the other hand, $IL\text{-}6^{high}$ patients with MSA, which were more obese, older, with higher neutrophil and basophil counts and TNF levels, displayed a decrease of miR-21-5p, miR-126-3p, and miR-146a-5p.

**Conclusion:** Immune-related miRNAs, including miR-21-5p, miR-126-3p, miR-146a-5p, and miR-215-5p can be used as clinically relevant non-invasive biomarkers of the phenotype/endotype and severity of asthma.

**Keywords:** asthma; biomarker; endotypes; miRNAs; phenotypes.

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Sci Rep

. 2022 Aug 15;12(1):13820.

doi: 10.1038/s41598-022-15612-w.

# FVC, but not FEV $_1$, is associated with clinical outcomes of asthma-COPD overlap

Tai Joon An [1], Chin Kook Rhee [2], Yong Bum Park [3], Kwang-Ha Yoo [4], Hyoung Kyu Yoon [5]

Affiliations expand

- PMID: 35970932

- PMCID: PMC9378661

- DOI: 10.1038/s41598-022-15612-w

## Abstract

The effects of forced vital capacity (FVC) on clinical outcomes of asthma-chronic obstructive pulmonary diseases overlap (ACO) are still unknown. We conducted this study to examine the association of FVC on clinical outcomes in ACO. Data from the Korean COPD Subgroup Study cohort were analyzed. Patients who fulfilled the ACO criteria were included and grouped according to FVC changes, such as FVC-incline and FVC-decline. No significant differences were observed between the FVC-incline and FVC-decline groups in baseline clinical characteristics. In a year after, FVC-decline group experienced more moderate (47.1% vs. 36.8%, p = 0.02) and moderate-to-severe (49.8% vs. 39.6%, p = 0.03) acute exacerbations (AEs), compared to FVC-incline group. The frequency of moderate AEs (1.3 ± 2.1 vs. 0.9 ± 1.7, p = 0.03) and moderate-to-severe AEs (1.5 ± 2.5 vs. 1.1 ± 1.9, p = 0.04) were higher in the FVC-decline group than in the FVC-incline groups. After adjusting

for confounding factors, FVC-decline group was associated with moderate AEs (odds ratio [OR] = 1.58; 95% confidence interval [CI] 1.02-2.44; p = 0.04), and moderate-to-severe AEs (OR = 1.56; 95% CI 1.01-2.41; p < 0.05) in ACO patients, which was not seen in $FEV_1$ changes. FVC changes are associated with clinical outcomes in ACO.

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## Conflict of interest statement

The authors declare no competing interests.

- 32 references
- 3 figures

SUPPLEMENTARY INFO

MeSH terms, Grant supportexpand

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21

Pediatrics

. 2022 Aug 16;e2021053507.

doi: 10.1542/peds.2021-053507. Online ahead of print.

# Use of a Clinical Guideline and Orderset to Reduce Hospital Admissions for Croup

Gabrielle Hester[1], Amanda J Nickel[2], David Watson[2], Walid Maalouli[3], Kelly R Bergmann[4]

Affiliations expand

- PMID: 35970819

- DOI: 10.1542/peds.2021-053507

# Abstract

**Background:** Studies have found infrequent interventions after croup admission. Our objectives were to achieve 25% reduction in (1) admission rate and (2) neck radiograph utilization among patients presenting to the emergency department.

**Methods:** At our tertiary children's hospital, we implemented clustered interventions including education, guideline, and orderset integration. We included patients 3 months to 8 years old with an emergency department, observation, or inpatient encounter for croup. We excluded patients with direct or ICU admissions, complex chronic conditions, or concurrent asthma, pneumonia, or bronchiolitis. We reviewed a random sample of 60% of encounters from baseline (October 1, 2017 to September 30, 2019) and implementation (October 1, 2019 to September 30, 2020) periods. We conducted a posthoc analysis from October 1, 2017 to December 1, 2021 to assess sustainment during coronavirus disease 2019. Interrupted time series analysis was used to evaluate changes in outcome, process, and balancing measures.

**Results:** There were 2906 (2123 baseline and 783 implementation) encounters included. Extrapolating preintervention trend estimates, the baseline admission rate of 8.7% decreased to 5.5% postintervention (relative decrease 37% [95% confidence interval: 8 to 66]) and sustained over 26 months after implementation. Admission rate in patients receiving 2 or fewer racemic epinephrine was significantly lower in implementation (1.7%) compared with baseline (6.3%), relative decrease of 72% (95% confidence interval: 68 to 88). There were no significant changes in neck radiographs, length of stay, or revisits.

**Conclusions:** Croup quality improvement interventions were associated with a significant decrease in hospital admissions with no increase in revisits.

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## Conflict of interest statement

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated they have no conflicts of interest to disclose.

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22

Inhal Toxicol

. 2022 Aug 15;1-11.

doi: 10.1080/08958378.2022.2110334. Online ahead of print.

# Development of a screening protocol to identify persons who are responsive to wood smoke particle–induced airway inflammation with pilot assessment of GSTM1 genotype and asthma status as response modifiers

Neil E Alexis[1,2], Laura Y Zhou[1,3], Allison J Burbank[2,4], Martha Almond[1], Michelle L Hernandez[2,4], Katherine H Mills[2], Terry L Noah[1,5], Heather Wells[1], Haibo Zhou[1,4], David B Peden[1,2]

Affiliations expand

- PMID: 35968917

- DOI: 10.1080/08958378.2022.2110334

## Abstract

**Background:** We are currently screening human volunteers to determine their sputum polymorphonuclear neutrophil (PMN) response 6- and 24-hours following initiation of exposure to wood smoke particles (WSP). Inflammatory responders (≥10% increase in %PMN) are identified for their subsequent participation in mitigation studies against WSP-induced airways inflammation. In this report we compared responder status ($N$ = 52) at both 6 and 24 hr time points to refine/expand its classification, assessed the impact of the GSTM1 genotype, asthma status and sex on responder status, and explored whether sputum soluble phase markers of inflammation correlate with PMN responsiveness to WSP.

**Results:** Six-hour responders tended to be 24-hour responders and vice versa, but 24-hour responders also had significantly increased IL-1beta, IL-6, IL-8 at 24 hours post WSP exposure. The GSTM1 null genotype significantly ($p$ < 0.05) enhanced the %PMN response

by 24% in the 24-hour responders and not at all in the 6 hours responders. Asthma status enhanced the 24 hour %PMN response in the 6- and 24-hour responders. In the entire cohort (not stratified by responder status), we found a significant, but very small decrease in FVC and systolic blood pressure immediately following WSP exposure and sputum %PMNs were significantly increased and associated with sputum inflammatory markers (IL-1beta, IL-6, IL-8, and PMN/mg) at 24 but not 6 hours post exposure. Blood endpoints in the entire cohort showed a significant increase in %PMN and PMN/mg at 6 but not 24 hours. Sex had no effect on %PMN response.

**Conclusions:** The 24-hour time point was more informative than the 6-hour time point in optimally and expansively defining airway inflammatory responsiveness to WSP exposure. GSTM1 and asthma status are significant effect modifiers of this response. These study design and subject parameters should be considered before enrolling volunteers for proof-of-concept WSP mitigation studies.

**Keywords:** Wood smoke particle exposure; airway neutrophil response; responder status.

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**RHINITIS**

Clin Exp Allergy

. 2022 Aug 20.

doi: 10.1111/cea.14218. Online ahead of print.

# Oxidative balance in subjects with allergic rhinitis: A nationwide cross-sectional survey

In Cheol Hwang[1], Hong Yup Ahn[2]

Affiliations expand

- PMID: 35986607

- DOI: 10.1111/cea.14218

*No abstract available*

**Keywords:** Allergic rhinitis; Cross-sectional studies; Oxidative stress; Population surveillance.

SUPPLEMENTARY INFO

Publication typesexpand

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Sci Rep

. 2022 Aug 18;12(1):14104.

doi: 10.1038/s41598-022-18443-x.

# HSP70 upregulation in nasal mucosa of symptomatic children with allergic rhinitis and potential risk of asthma development

Anna Fagotti[#1], Livia Lucentini[#2], Francesca Simoncelli[1], Gianandrea La Porta[1], Leonardo Brustenga[1], Ilaria Bizzarri[3], Silvia Trio[3], Chiara Isidori[3], Ines Di Rosa[1], Giuseppe Di Cara[3]

Affiliations expand

- PMID: 35982171

- PMCID: PMC9388484

- DOI: 10.1038/s41598-022-18443-x

# Abstract

Allergic rhinitis and asthma are the most common causes of chronic inflammation of the upper and lower airways in childhood. However, a nasal biomarker that can link to pulmonary inflammation is yet to be found. The present paper aims to investigate the possible role in inflammation of two inducible 70-kDa Heat Shock Proteins (HSP70) members, HSPA1A/B and HSPA6, in nasal mucosa cells of allergic children through their mRNA expression analysis, and their correlation to both spirometric and FeNO values. The relationship between FeNO in lower airways and ΔCts of HSPA1A/B in nasal mucosa seems to be influenced by clinical symptoms regardless of age, sex, and sensitization patterns. Therefore, HSP70 expression, as well as FeNO levels, could have a predictive capability to identify lower airways inflammation and thus to recognize rhinitic children having a potential risk of asthma development.

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## Conflict of interest statement

The authors declare no competing interests.

- 50 references
- 6 figures

SUPPLEMENTARY INFO

Grant supportexpand

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Review

J Allergy Clin Immunol

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. 2022 Aug 15;S0091-6749(22)00915-0.

doi: 10.1016/j.jaci.2022.06.023. Online ahead of print.

# The role of the CBM complex in allergic inflammation and disease

Stanley B DeVore[1], Gurjit K Khurana Hershey[2]

Affiliations expand

- PMID: 35981904

- DOI: 10.1016/j.jaci.2022.06.023

## Abstract

The caspase activation and recruitment domain-coiled-coil (CARD-CC) family of proteins-CARD9, CARD10, CARD11, and CARD14-is collectively expressed across nearly all tissues of the body and is a crucial mediator of immunologic signaling as part of the CARD-B-cell lymphoma/leukemia 10-mucosa-associated lymphoid tissue lymphoma translocation protein 1 (CBM) complex. Dysfunction or dysregulation of CBM proteins has been linked to numerous clinical manifestations known as "CBM-opathies." The CBM-opathy spectrum encompasses diseases ranging from mucocutaneous fungal infections and psoriasis to combined immunodeficiency and lymphoproliferative diseases; however, there is accumulating evidence that the CARD-CC family members also contribute to the pathogenesis and progression of allergic inflammation and allergic diseases. Here, we review the 4 CARD-CC paralogs, as well as B-cell lymphoma/leukemia 10 and mucosa-associated lymphoid tissue lymphoma translocation protein 1, and their individual and collective roles in the pathogenesis and progression of allergic inflammation and 4 major allergic diseases (allergic asthma, atopic dermatitis, food allergy, and allergic rhinitis).

**Keywords:** Allergy; BCL10; CARD; CARD10; CARD11; CARD14; CARD9; CBM-opathy; MALT1; allergic rhinitis; asthma; atopic dermatitis; food allergy.

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Int Forum Allergy Rhinol

. 2022 Aug 18.

doi: 10.1002/alr.23059. Online ahead of print.

# A Comparative Analysis of Endoscopic Sinus Surgery Versus Biologics for Treatment of Chronic Rhinosinusitis with Nasal Polyposis

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Affiliations expand

- PMID: 35980852

- DOI: 10.1002/alr.23059

## Abstract

**Background:** Comparative effectiveness research between endoscopic sinus surgery(ESS) and biologic therapy for severe chronic rhinosinusitis with nasal polyposis(CRSwNP) is a nascent field as new therapeutic modalities become clinically available.

**Methods:** A prospective, multi-center cohort of CRSwNP patients, undergoing ESS between 2011-2019, were compared to Phase-3 biologic trial data. Patients undergoing ESS received baseline nasal endoscopy quantified via Lund-Kennedy(LK) grading. Patients meeting inclusion criteria, modified from dupilumab-LIBERTY-NP-24&52, omalizumab-POLYP-1&2, and mepolizumab-SYNAPSE clinical trials, were included in this study. Baseline

characteristics and outcome measures were compared between these cohorts at 24-weeks and 52-weeks, when possible.

**Results:** One-hundred eleven CRSwNP patients met modified inclusion criteria. There were no statistically significant differences in baseline age, sex, asthma status, aspirin-exacerbated respiratory disease status, smell identification, LK-polyp score, and Lund-Mackay CT scores between ESS and biologic groups. At 24-weeks, ESS demonstrated significantly greater improvements in Sino-Nasal Outcome Test-22(SNOT-22) compared to one (of two) dupilumab trials($p < 0.05$) and both omalizumab trials($p < 0.001$). ESS associated with significantly lower nasal polyp scores(NPS) compared to dupilumab($p < 0.001$) and omalizumab($p < 0.001$), despite comparable improvements in smell identification($p > 0.05$). At 52-weeks, ESS resulted in statistically similar improvement in SNOT-22 scores compared to dupilumab($p = 0.21$), but NPS remained significantly lower in the ESS group compared to dupilumab($p < 0.001$) and mepolizumab($p < 0.001$).

**Conclusions:** At 24-weeks and 52-weeks, ESS offers comparable SNOT-22 improvements compared to dupilumab. ESS and dupilumab offer comparable improvement in smell identification at 24-weeks. Compared to omalizumab, ESS offers superior SNOT-22 improvements. ESS offers significantly greater reductions in polyp size compared to omalizumab, dupilumab, and mepolizumab therapies. This article is protected by copyright. All rights reserved.

**Keywords:** chronic rhinosinusitis; endoscopic sinus surgery; eosinophilic rhinitis and nasal polyposis.

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Allergy

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. 2022 Aug 18.

doi: 10.1111/all.15485. Online ahead of print.

# Validated allergen exposure chamber is plausible tool for assessment of house dust mite–triggered allergic rhinitis

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- PMID: 35980665

- DOI: 10.1111/all.15485

## Abstract

**Background:** Allergen exposure chamber (AEC) is a clinical facility that allows exposure to allergenic airborne particles in controlled environment. Although AECs offer stable levels of airborne allergens, the validation of symptoms and other endpoints induced by allergen challenge is key for their recommendation as a plausible tool for the assessment of patients, especially in clinical research. This study aimed to demonstrate the reproducibility of defined clinical endpoints after AEC house dust mite (HDM) challenge under optimal conditions in patients with allergic rhinitis (AR).

**Method:** HDM was distributed at different concentrations. The assessment was subjective by the patients: total nasal symptom score (TNSS), visual analogue scale (VAS) and objective by the investigator: acoustic rhinometry, peak nasal inspiratory flow (PNIF), and nasal secretion weight. Safety was assessed clinically and by peak expiratory flow rate (PEFR) and forced expiratory volume in the first second ($FEV_1$ ).

**Results:** Constant environment: temperature, humidity, and carbon dioxide ($CO_2$ ) concentration were maintained during all challenges. The concentration of HDM on average remained stable within the targeted values: 1,000, 3,000, 5,000, 7000 particles (p)/ $m^3$ . Most symptoms were observed at concentrations 3,000 p/ $m^3$ or higher. The symptoms severity and other endpoints results were reproducible. 5,000 p/ $m^3$ and challenge duration of 120 minutes were found optimal. The procedure was safe with no lung function abnormalities due to challenge.

**Conclusion:** HDM challenge in ALL-MED AEC offers a safe and reliable method for inducing symptoms in AR patients for the use in controlled clinical studies including allergen immunotherapy.

**Keywords:** acoustic rhinometry; allergen challenge; allergen exposure chamber (AEC); allergic rhinitis (AR); house dust mite (HDM).

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Free Radic Biol Med

. 2022 Aug 20;189:85-90.

doi: 10.1016/j.freeradbiomed.2022.07.008. Epub 2022 Jul 19.

# The association between prenatal $F_2$-isoprostanes and child wheeze/asthma and modification by maternal race

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- PMID: 35863687

- DOI: 10.1016/j.freeradbiomed.2022.07.008

## Abstract

**Background:** Childhood wheeze, asthma, and allergic rhinitis are common and likely have prenatal origins. Oxidative stress is associated with respiratory disease, but the association of oxidative stress during the prenatal period with development of respiratory and atopic disease in childhood, particularly beyond the infancy period, is unknown. This study aims to investigate associations between prenatal oxidative stress, measured by maternal

urinary $F_2$-isoprostanes, and child respiratory outcomes, including effect modification by maternal race.

**Methods:** We prospectively studied Black (n = 717) and White (n = 363) mother-child dyads. We measured $F_2$-isoprostanes in 2nd-trimester urine (ng/mg-creatinine). At approximately age 4, we obtained parent report of provider-diagnosed asthma (ever), current wheeze, current asthma (diagnosis, symptoms and/or medication), and current allergic rhinitis (current defined as previous 12 months). We used multivariable logistic regression to estimate adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) per interquartile range (IQR) increase in $F_2$-isoprostane concentration, controlling for confounders. We examined modification by maternal race using interaction terms.

**Results:** The prevalence of provider-diagnosed asthma and current wheeze, asthma and allergic rhinitis was 14%, 19%, 15%, and 24%, respectively. Median (IQR) $F_2$-isoprostane levels were 2.1 (1.6, 2.9) ng/mg-creatinine. Associations between prenatal $F_2$-isoprostanes and provider-diagnosed asthma, current wheeze, and current asthma were modified by maternal race. Results were strongest for current wheeze (aOR [95%CI]: 1.55 [1.16, 2.06] for White; 0.98 [0.78, 1.22] for Black; p-interaction = 0.01). We observed no association between $F_2$-isoprostanes and allergic rhinitis.

**Conclusion:** Prenatal urinary $F_2$-isoprostanes may be a marker associated with childhood wheeze/asthma in certain populations. Research is needed to understand underlying mechanisms and racial differences.

**Keywords:** Allergic rhinitis; Asthma; Isoprostane; Oxidative stress; Pediatric; Prenatal; Wheezing.

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Altern Ther Health Med

. 2022 Aug 19;AT7561.

Online ahead of print.

# Efficacy and Safety Analysis of Piperacillin Tazobactam in Combination With High Frequency Chest Wall Oscillation in Patients With COPD Coupled With Pneumonia

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- PMID: 35986739

## Abstract

**Context:** Chronic obstructive pulmonary disease (COPD) is a common, chronic inflammatory disease of the airway, and acute exacerbation of COPD (AE-COPD) refers to the manifestations of inflammation in the lungs that appear within a short period of time. Some patients contract pneumonia, and they can be prone to recurrent attacks of AE-COPD combined with pneumonia. The efficacy of conventional treatments isn't generally satisfactory.

**Objective:** The study intended to investigate the effectiveness and safety of piperacillin tazobactam in combination with the use of high-frequency chest-wall oscillation (HFCWO) to produce expectoration for the treatment of pneumonia in patients with AE-COPD and to provide a reference for clinical treatment.

**Design:** The research team designed a prospective, randomized controlled trial.

**Setting:** The study took place at the Sixth Hospital of Wuhan of the Affiliated Hospital of Jianghan University in Wuhan, China.

**Participants:** Participants were 92 patients who had been admitted to the hospital between January 2020 and November 2021 with AE-COPD combined with pneumonia.

**Intervention:** Using the random number table method, the research team randomly assigned participants to one of two groups, an intervention group or a control group, each with 46 participants. The control group received conventional treatment with oxygen, antibiotics, antispasmodics, antiasthmatic drugs, and phlegmolytic drugs as well as HFCWO for sputum removal. In addition to those treatments, the intervention group received piperacillin tazobactam.

**Outcome measures:** The research team measured the treatment's efficacy at one day postintervention. At baseline and at one day postintervention, the study also measured pulmonary function, laboratory indexes, and blood-gas-analysis indexes. In addition, the research team identified the time of disappearance of clinical symptoms, including the disappearance of cough, sputum, dyspnea, and pulmonary rales; calculated the length of hospital stay, and evaluated the treatment's safety.

**Results:** Postintervention, the intervention group's clinical efficacy was significantly higher than that of the control group ($P < .05$), and the group's cough, coughing of sputum, dyspnea, disappearance time of pulmonary rales, and hospitalization times were all significantly lower than those in the control group ($P < .05$). The FEV1, FVC, FEV1% and FEV1/FVC levels were higher in both groups postintervention than at baseline and were significantly higher in the intervention group than in the control group ($P < .05$). Postintervention, the levels of IL-2, IL-10, TNF-α, CRP and PCT were lower in both groups than at baseline, and the intervention group's levels were significantly lower than those in the control group ($P < .05$). Postintervention, the $PaCO_2$ level decreased and $PaO_2$ and $SaO_2$ levels increased in both groups compared to baseline; the intervention group's $PaCO_2$ level was lower and $PaO_2$ and $SaO_2$ levels were higher than those in the control group. During the treatment, no adverse reactions occurred in the control group, and one participant had a decreased appetite in the intervention group; the incidence of adverse reactions in that group was 2.17% (1/46). That participant received no special treatment, and the condition improved after stopping the drug.

**Conclusion:** Piperacillin tazobactam combined with HFCWO for sputum evacuation can effectively treat patients with pneumonia in acute exacerbation of COPD, with high safety. The treatment is worthy of clinical application.

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. 2022 Aug 15.

doi: 10.1007/s41030-022-00193-w. Online ahead of print.

# Treatment with the P2X3-Receptor Antagonist Gefapixant for Acute Cough in Induced Viral Upper Respiratory Tract Infection: A Phase 2a, Randomized, Placebo-Controlled Trial

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Affiliations expand

- PMID: 35969360

- DOI: 10.1007/s41030-022-00193-w

## Abstract

**Introduction:** Available therapies for acute cough, a condition frequently caused by a viral upper respiratory tract infection (URTI), have shown limited evidence of efficacy. Gefapixant, a P2X3-receptor antagonist, has demonstrated efficacy and safety in studies of the treatment of refractory or unexplained chronic cough, but its efficacy for treating acute cough has not been previously studied.

**Methods:** This was a phase 2a, randomized, double-blind, placebo-controlled, parallel-group, pilot study. Healthy volunteers were randomized 1:1 to receive twice-daily gefapixant 45 mg or placebo and inoculated with human rhinovirus 16 to induce URTI and cough. Participants were observed while quarantined for 7 days after the start of treatment. The primary endpoint was awake cough frequency on day 3, which was objectively measured with a cough-recording device. Secondary endpoints included change from baseline to day 3 in subjective cough severity measures (cough severity visual analog scale, Cough Severity Diary) and cough-specific quality of life (Leicester Cough Questionnaire-acute).

**Results:** Of the 46 participants who met inclusion criteria [mean (standard deviation, SD) age, 24.6 (6.5) years; females, n = 8], 40 completed the study (gefapixant, n = 21; placebo,

n = 19). There was no significant difference in awake cough frequency on day 3 between the gefapixant and placebo groups [least squares means, 2.4 versus 2.7 coughs per hour, respectively; mean difference (95% confidence interval, CI), -0.3 (-2.3, 1.7); P = 0.75]. There were no significant between-group differences for any of the secondary endpoints. Peak cough frequency was low and occurred later in the study than expected (days 4-5). The safety profile was consistent with that of previous studies of gefapixant.

**Conclusion:** Compared with placebo, gefapixant did not reduce the frequency or severity of acute cough secondary to induced URTI. Induced viral URTI produced mild symptoms, including lower cough frequency than observed in previous studies of patients selected for acute cough associated with naturally occurring URTI.

**Trial registration:** ClinicalTrials.gov, NCT03569033; EudraCT, 2017-000472-28; protocol number, MK-7264-013.

**Keywords:** Acute cough; Antitussives; Common cold; Cough frequency; P2X3-receptor antagonists; URTI.

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