



Contents lists available at ScienceDirect

Allergy International

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Invited Review Article

Asthma and COPD overlap pathophysiology of ACO

Mari Hikichi, Shu Hashimoto*, Yasuhiro Gon

Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:

Received 3 December 2017

Received in revised form

21 December 2017

Accepted 27 December 2017

Available online xxx

Keywords:

ACO

Asthma

British hypothesis

COPD

Dutch hypothesis

ABSTRACT

Asthma and COPD appear as a result of different mechanisms triggered by different pathogeneses and although they present different features and symptoms of airway inflammation and airway obstruction, there are also cases that present the features of both asthma and COPD. This type of pathology is known as asthma-COPD overlap syndrome (ACOS). Asthma-COPD overlap is identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms". In this paper, the disease that shares several features of both asthma and COPD will be referred to as asthma-COPD overlap (ACO). In this article, we describe the pathogenesis of ACO for understanding the mechanism in asthma and COPD overlap.

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Introduction

Bronchial asthma (asthma) is defined as follows: "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation".¹ And chronic obstructive pulmonary disease (COPD) is defined as follows: "Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".² Asthma and COPD appear as a result of different mechanisms triggered by different pathogeneses and although they present different features and symptoms of airway inflammation and airway obstruction, there are also cases that present the features of both asthma and COPD. This type of pathology is known as asthma-COPD overlap syndrome (ACOS). In 2014 the GINA & GOLD Joint Committee defined it as follows: "Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the

features that it shares with both asthma and COPD".³ However, subsequently for a variety of reasons the term "syndrome" – a term that is normally used to refer to an idiopathic (in some cases, the term continues to be used even after the cause is identified) pathology with features in common (e.g. clinical symptoms, test findings) – came to be considered inappropriate in this context. Those reasons included the fact that the pathogeneses of asthma and COPD are not a single phenomenon but rather are formed due to a variety of mechanisms and the fact that the clinical features are highly diverse. As a result, it has been recommended that the term "syndrome" be dropped and that the disease name be changed to "asthma and COPD overlap (ACO)". The disease then was described as follows: "Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD. This is not a definition, but a description for clinical use, as asthma-COPD overlap includes several different clinical phenotypes and there are likely to be several different underlying mechanisms".¹ In this paper, the disease that shares several features of both asthma and COPD will be referred to as ACO.

History

It was previously known that a disease that shared the features of both asthma and COPD existed, but it was described using a variety of names. For example, the American Thoracic Society used a Venn diagram to identify the existence of a disease with

* Corresponding author. Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Ohayaguchikamimachi, Itabashi-ku Tokyo 173-8610, Japan.

E-mail address: hashimoto.shu@nihon-u.ac.jp (S. Hashimoto).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2018.01.001>

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overlapping features of emphysema, chronic bronchitis, and asthma. It described this disease as follows: “Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and in Fig. 1).”⁴ Subsequently, interest in such cases increased and research that analyzed its pathophysiology and clinical features reached a peak in activity.

Overlapping mechanisms

The overlapping mechanisms hypothesis

Two explanations of the mechanism by which a disease with the characteristics of both asthma and COPD forms have been proposed: The Dutch Hypothesis and the British Hypothesis.

1) The Dutch Hypothesis

The Dutch Hypothesis was first proposed by the Dutch researcher Dick Orie in 1961. He hypothesized that “asthma, chronic bronchitis, and pulmonary emphysema (COPD) is a single disease (chronic non-specific disease) that occurs as a result of the same genetic factors (atopic status, promotion of airway hyperreactivity), and only presents different clinical phenotypes due to different environmental factors (allergens, smoking, and infections).” This

hypothesis was referred to as the Dutch Hypothesis by Fletcher, who laid the basis for the disease concept of chronic non-specific lung disease (CNLD).⁵ According to this hypothesis, an individual with certain genetic factors presents the clinical phenotype of COPD when exposed to smoking and the clinical phenotype of asthma when exposed to allergens. Additionally, there is ACO, which is characterized by the fact that the patient has features of both COPD and asthma as a result of having been exposed to both environmental factors and therefore the two cannot be separated (as described by Orie *et al.*).

2) The British Hypothesis

The British Hypothesis was first proposed in 1965 by Charles Fletcher, who described it as “A disease in which asthma and COPD occur as a result of different mechanisms triggered by different pathogeneses”.⁶ Unlike the Dutch Hypothesis in which asthma and COPD are described as being impossible to separate, the British Hypothesis proposes that ACO is a pathophysiology that has features of both asthma and COPD in cases in which factors such as smoking contribute to asthma and in cases in which factors related to asthma, including antigen sensitization, contribute to COPD.

The major cause of COPD onset is smoking. However, only approximately 10%–15% of smokers develop COPD. This is thought to be due to whether or not the individual has disease susceptibility genes for smoking and other factors in addition to smoking. Genetic and other factors identified in smokers who experience major decreases in respiratory function over time include airway hyperreactivity, peripheral eosinophilia, and elevated IgE. In addition, it has been indicated that, in addition to smoking, COPD onset requires genetic factors such as atopy and promotion of airway hyperreactivity. In other words, individuals who have these genetic factors will develop COPD as a result of smoking. In contrast, those who are exposed to allergens or allergen stimulation will develop bronchial asthma.

As the validity of the Dutch and British hypotheses as regards the mechanism by which features of both asthma and COPD are presented simultaneously are still subject to debate, no conclusion has yet been reached.

Factors that tend to increase the probability of asthma and COPD overlap

Factors that tend to increase the probability of asthma and COPD overlap – i.e. risk factors – include atopy and airway hyperreactivity. Promotion of airway hyperreactivity, which is a feature of the pathophysiology of asthma, is a risk factor for COPD. Pulmonary hypoplasia, which is greatly affected by the intrauterine environment and the external environment up to the age of 5 years, is a risk factor for both asthma and COPD. Thus, in the presence of these risk factors, the probability of asthma and COPD overlap onset tend to increase.

1) Airway hyperreactivity

Orie *et al.* indicated that airway hyperreactivity, which is a genetic condition, is a risk factor that is common to both asthma and COPD onset. Research outcomes that support this hypothesis are as follows. A 24-year-long follow-up study of healthy adults that investigated the relation of airway hyperreactivity to the appearance of symptoms such as coughing, phlegm, difficulty breathing, and asthma attacks indicated that airway hyperreactivity was a predictive factor for the appearance of those symptoms. In addition, airway hyperreactivity is a factor that accelerates decreased pulmonary function (estimated %FEV_{1.0}; Fig. 2).⁷

Airway hyperreactivity is regulated by both reversible and irreversible factors. The reversible factors include mediators that accompany airway inflammation and changes in the autonomic nervous system. Irreversible factors include changes in airway diameter. The reversible factors are associated with airway

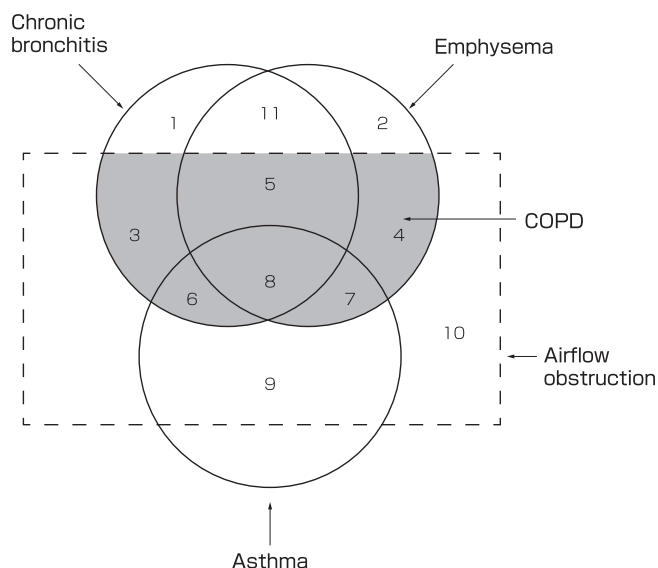


Fig. 1. Non-proportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society. The subsets comprising COPD are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction although, in variant asthma, special manoeuvres may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2 and 11) are not classified as having COPD. Patients with airflow obstruction due to diseases with known aetiology or specific pathology such as cystic fibrosis or obliterative bronchiolitis (subset 10) are not included in this definition.

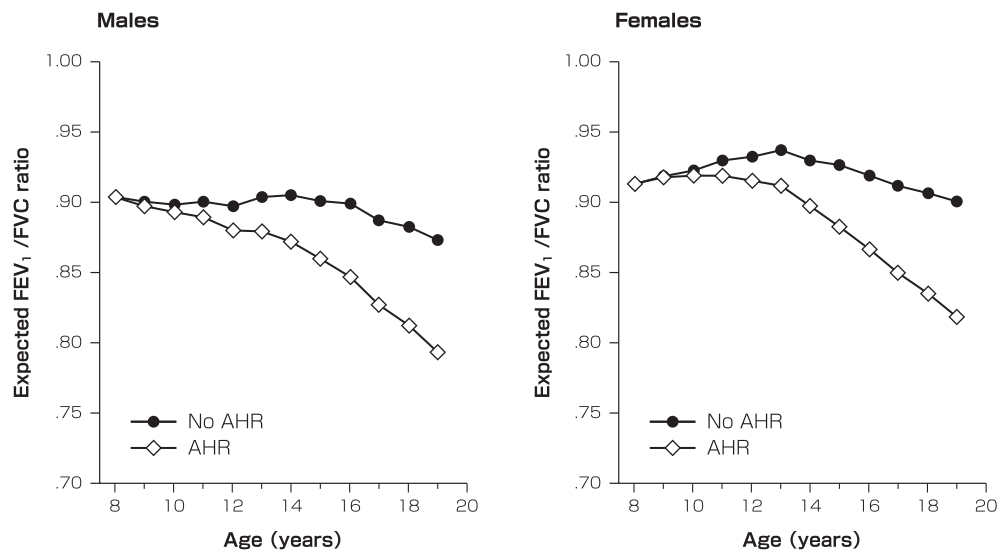


Fig. 2. Growth pattern of expected FEV₁/FVC ratio in boys and girls with and without AHR. Expected FEV₁/FVC ratio was calculated as the ratio of expected FEV₁ and expected FVC.

hyperreactivity caused by airway inflammation in cases of asthma. The irreversible factors are associated with constricted airway diameter caused by airway remodelling in cases of asthma or constricted airway diameter caused by histopathological changes in cases of COPD.⁸ It has been reported that in cases of COPD neutrophilic inflammation is also related to airway hyperreactivity.¹⁰ In general, airway diameter is a regulatory factor for COPD-related airway hyperreactivity⁸ (Fig. 3), but since airway hyperreactivity is

related to accelerated pulmonary function decrease, the acceleration may more likely result in obstructive ventilatory defect. Moreover, atopy has been alternately reported to be a risk factor for COPD onset and not a risk factor for COPD onset.¹⁰

2) Genetic background

Genetic analysis associated with asthma and COPD onset has identified several disease susceptibility genes that are common to both asthma and COPD. In recent years, comprehensive genetic analysis had led to the identification of disease susceptibility genes associated with COPD and asthma, and the functions of these genes are currently in the process of being elucidated.¹¹ Orie sought a common genetic factor for both atopy and promotion of airway hyperreactivity, and Orie's hypothesis was confirmed by molecular functions elucidated by comprehensive analysis of disease susceptibility genes and molecular biological techniques. What follows is a description of some of those molecules.

(1) ADAM33 (A Disintegrin and Metalloprotease Domain)

The ADAM gene is a gene that encodes the ADAM (A Disintegrin and Metalloprotease Domain) family of genes. It suppresses cell–cell and cell–matrix interactions and is related to a variety of biological process, including fertilization, muscle development, and neurogenesis. In recent years, the ADAM gene has been identified as a gene related to asthma susceptibility and airway hyperreactivity.¹² ADAM33 is expressed in tracheal smooth muscle and epithelial cells and is involved in airway remodelling. The ADAM33 genotype is related to pulmonary function in infancy, the course of pulmonary function in cases of bronchial asthma, and the course of pulmonary function in cases of COPD.^{13,14}

(2) Orosomucoid like 3 (ORMDL3)

ORMDL3 is present in endoplasmic reticulum (ER) membranes. It is a membrane protein that contributes to the accumulation of proteins with folding anomalies or structural anomalies (unfolded protein) in the ER as a result of intra- and extracellular stimuli that inhibit protein modification, i.e. a membrane protein involved in ER stress response. When under ER stress, GRP78/BiP separates, ATF6, IRE, and PERK are activated, and metalloproteases (MMP-9, ADAM-8), CC chemokines (CCL-20), CXC chemokines (IL-8, CXCL-10, CXCL-11), oligoadenylate synthetases (OAS) genes, and SERCA2b are expressed.^{15,16} Genome-wide association (GWA) analysis has identified *ORMDL3* as a gene that is related to paediatric asthma.¹⁸ *ORMDL3* expression is promoted by smoking, antigen stimulus, and IL-4/IL-13 stimulus.¹⁶

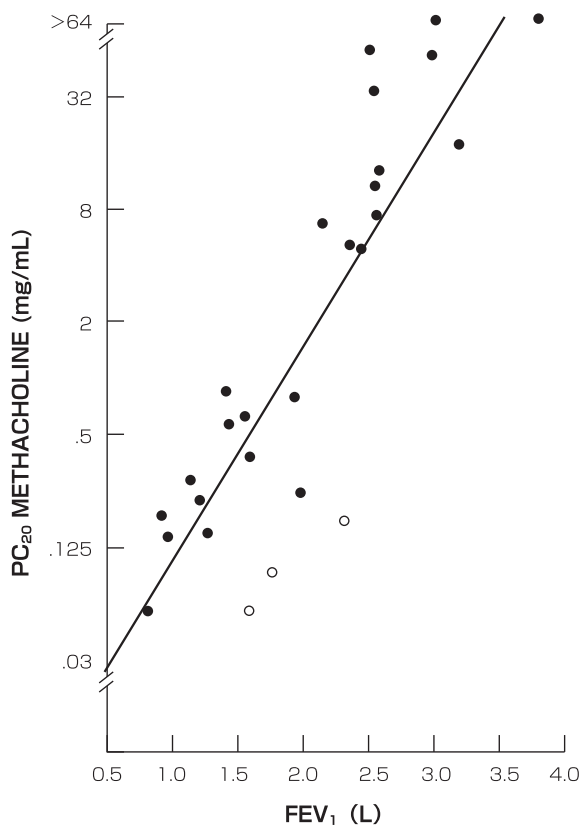


Fig. 3. Relationship between air flow obstruction and FEV₁, bronchial responsiveness to methacholine (PC₂₀, mg/mL). Patients responsive to cold air. The solid line represents the regression line ($r = 0.86$, $p < 0.001$).

Table 1
Risk factors for chronic obstructive pulmonary disease that have a role during different stages of life.

Host factors	Childhood exposure
- Family history of COPD - Family history of asthma/atopy - Genetic constitution - Bronchial hype-responsiveness - Atopy - Low lung function	- Respiratory tract infection - Maternal smoking - Indoor and outdoor pollution - Obesity/nutritional development - Childhood asthma - Airway failure to thrive
Prenatal factors	Adult exposures
- Maternal smoking - Maternal exposure to air pollution - Antibiotic use - Mode of delivery - Preterm birth - Childhood exposures	- Occupational exposures - Indoor biomass exposure - Cigarette smoking - Outdoor air pollution - Indoor air pollution

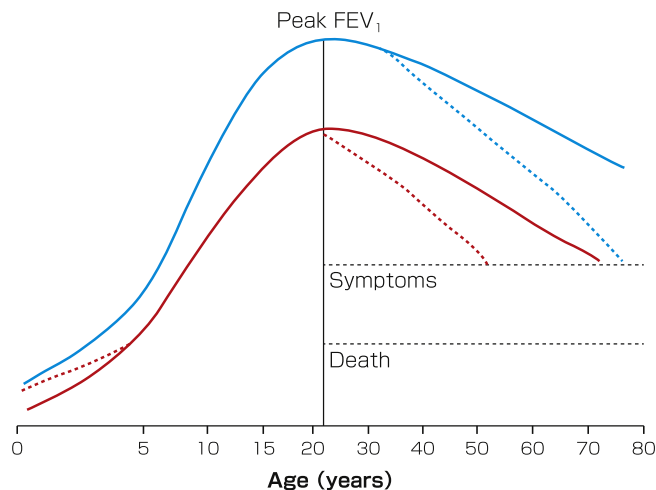


Fig. 4. Early origins of adult lung disease. In healthy children, continuous growth of the lungs and thorax throughout childhood results in maximum lung function at around 22 years of age (solid blue line). Subsequently, despite gradual age-related changes, considerable reserves are maintained into old age unless there is an accelerated rate of decline (dashed blue line) because of, for example, the effects of smoking. If a child is born with either suboptimum lung function due to intrauterine insults (red solid line), or has impaired airway lung and airway growth during the first 5 years of life (dashed red line) because of early postnatal insults, lung function might remain diminished throughout childhood. Failure to achieve optimal lung function as a young adult means that even in the absence of any further insults, such individuals will be prone to developing symptomatic respiratory disease as they age. Onset of such symptoms can occur much earlier in the presence of any additional risk factors for accelerated lung ageing (red dashed line).

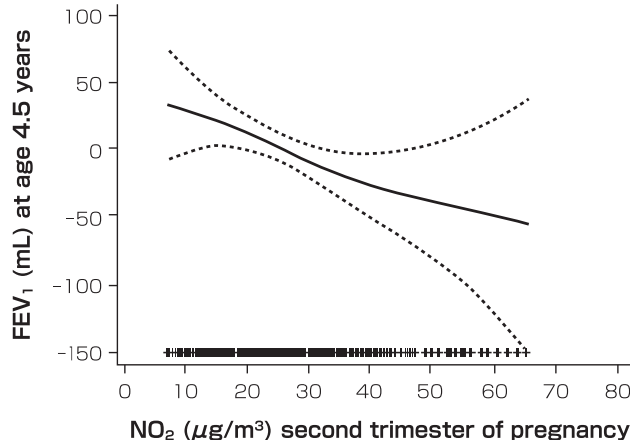
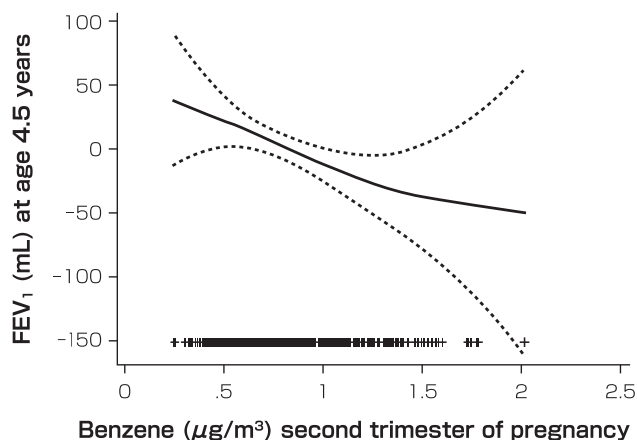


Fig. 5. The relation (and 95% confidence levels) of air pollutant levels during the second trimester of pregnancy with FEV₁ in preschoolers aged 4.5 years. General additive models adjusted for area of study, child's sex, and child's age, height and weight at assessment and ethnic background, birth weight, maternal social class, maternal education level, maternal smoking in pregnancy and paternal smoking in pregnancy, environmental tobacco smoke 0–14 months, and lower respiratory tract infections 0–14 months. The symbols (+) on the X-axis indicate air pollutant observations.

(3) IL-17

IL-17 is produced by Th17 cells that were differentiated and induced from Th0 by TGFβ. IL-17 plays an important role in the onset of neutrophilic inflammation in cases of bronchial asthma and is involved in matrix metalloproteases (MMP) from macrophages in cases of COPD. MMP are related to the formation of COPD lesions, and the MMP-12 polymorphism is related to the onset of COPD.¹⁸

3) Viral infection

Viral infections during early childhood are risk factors for the onset of asthma and COPD. As mentioned above, ORMDL3 is a factor that increases the likelihood of viral infections during early childhood. ORMDL3 is also a risk factor for bronchiolitis caused by rhinovirus infection and for the onset of asthma.¹⁹

4) Pulmonary hypoplasia

Genetic factors and growth promoting factors influence the growth of the airway and lungs from the time a child is still in the uterus until the age of five years, with bronchus and lung growth continuing until it reaches its maximum level of development at around the age of 22²⁰ (Fig. 4). Dysfunctional bronchus and lung growth particularly during the period of time from the fetal period until the age of five years has an effect on airway and lung growth during childhood and youth, and this may lead to the so-called “reduced lung growth” that occurs when the lungs are smaller as compared to the maximum under normal growth at around the age of 22. Respiratory function is also reduced as compared to normal FEV₁. Thereafter (i.e. after the age of 22), respiratory function continues to gradually decline year by year (Fig. 4). The factors that affect lung growth and respiratory function²¹ are shown in Table 1. Impeded growth of the airway and lungs caused by a variety of factors associated with an early life event – that is, from the fetal stage to early childhood – of asthma and COPD is related to subsequent onset of asthma and COPD. For example, smoking by the mother during the child's fetal stage is a risk factor for onset of paediatric asthma, and paediatric asthma is a risk factor for onset of COPD.

(1) Lung growth during the fetal stage/early childhood and respiratory dysfunction

a) During pregnancy

Atmospheric contaminants (benzene concentration, nitric oxide concentration) during mid-pregnancy is related to respiratory function at the age of 4 years 6 months, with higher concentrations leading to reduced respiratory function²² (Fig. 5). This type of respiratory dysfunction during early childhood leads to “reduced lung

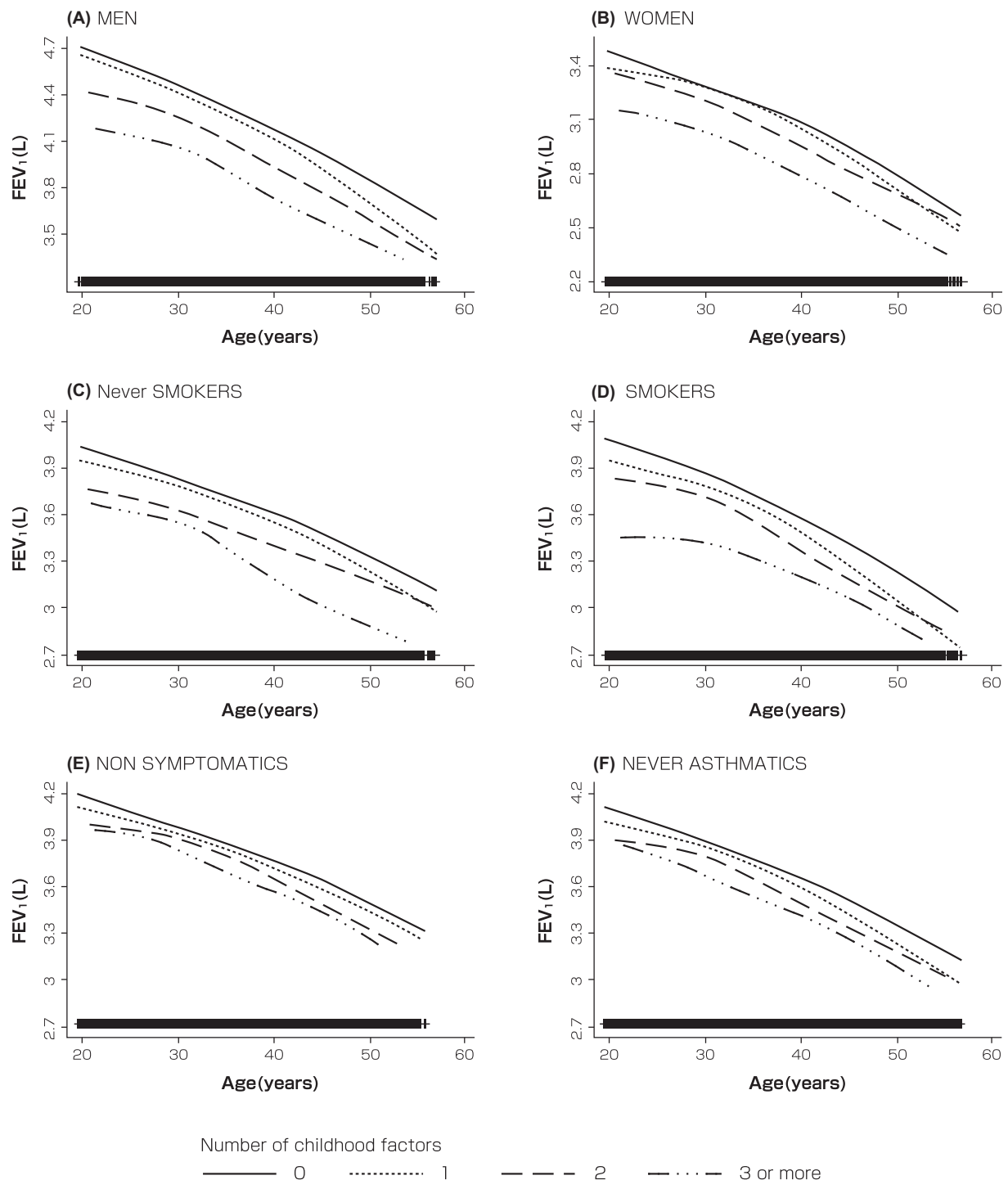


Fig. 6. Forced expiratory volume in 1 s (FEV₁) by age according to number of childhood disadvantage factors in (A) men and (B) women (adjusted for smoking and height); in (C) never smokers and (D) current smokers (adjusted for sex and height); and in (E) non-symptomatic subjects and (F) subjects who had never had asthma (childhood asthma excluded from childhood disadvantage factors) (adjusted for smoking, sex, and height). The curves were fitted using generalised additive models, based on FEV₁ measurements from both ECRHS I and ECRHS II for the age range 26–44 years, only ECRHS I measurements at ages 20–26 years and only ECRHS II measurements at age 45–56 years.

growth and function” during adulthood, when these concentrations reach their highest levels and is a risk factor for the onset of COPD.

b) Risk factors during pregnancy and early childhood

A study of the respiratory function of adults aged between 20 and 45 years at the start of the survey and again nine years later that investigated the relation between risk factors during

pregnancy and early childhood (asthma in the mother, asthma in both parents, paediatric asthma, smoking by the mother, and respiratory infections during early childhood) and the course of respiratory function during and after adulthood found that the number of risk factors during pregnancy and early childhood influenced decreases in respiratory function during adulthood, when respiratory function is at its peak, and later in life, regardless

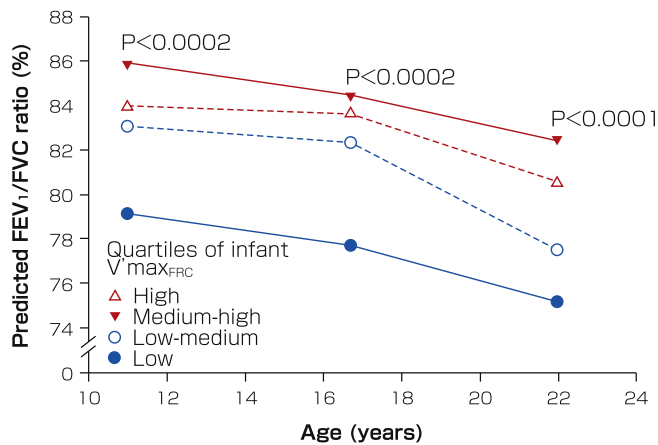


Fig. 7. Predicted mean values for lung function in males at ages 11, 16, and 22 years by length-adjusted infant VmaxFRC. Predicted values were standardised to the mean height and weight for male participants at ages 11, 16, and 22 years. We included an interaction term between survey (age 11, 16, and 22) and quartiles of infant VmaxFRC in the random-effects models. P values were estimated at each survey from the models.

of sex, smoking, symptoms, and presence or absence of asthma²³ (Fig. 6).

c) The relation between respiratory function immediately after birth and respiratory function at age 22

The Tucson Children's Respiratory Study investigated the changes in respiratory function at ages 11, 16, and 22 after dividing patients into four groups (High, Medium-high, Medium-low, Low) based on the respiratory function outcomes at the age of two months, which reflects the lung and respiratory function during the fetal stage. The results indicated that respiratory function at the age of two months was reflected in the respiratory function at the age of 22 years²⁴ (Fig. 7).

d) Changes in respiratory function from the early childhood stage to adulthood and thereafter

The CAMP study analyzed the factors that influence and changes FEV₁ in 684 children aged between 5 and 12 years until they reached adulthood (mean age of 26)²⁵ (Fig. 8). The results indicated that reduced growth was related to factors such as low FEV₁ at the time of participation in the study, reduced bronchodilation response,

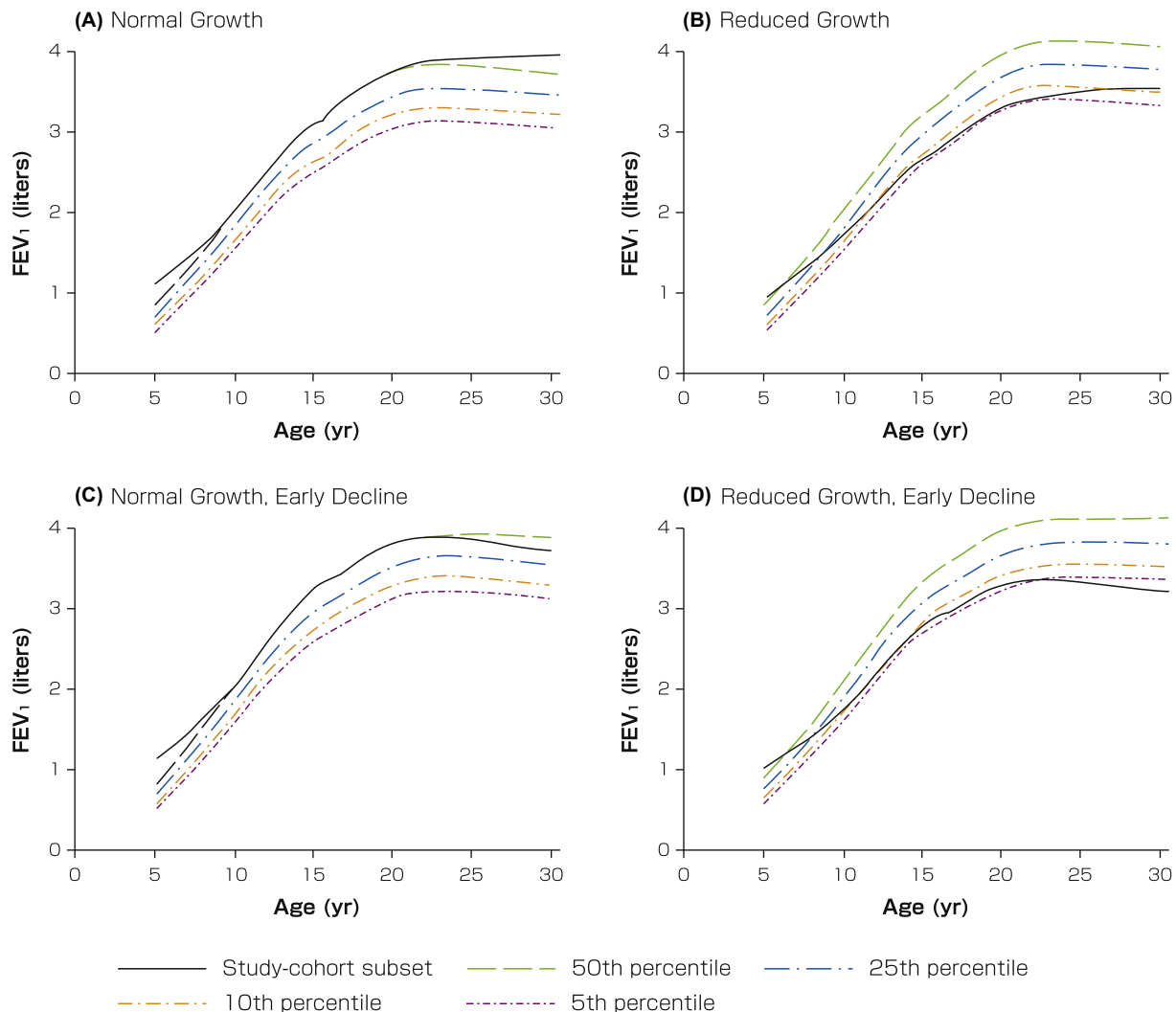


Fig. 8. Average Prebronchodilator FEV₁ Trajectories for 684 Study Participants According to Pattern Classification, as Compared with FEV₁ in Persons without Asthma. Values for prebronchodilator FEV₁ in the study participants are group averages and are based on robust, locally weighted scatterplot smoothing regression. Also shown are percentiles of FEV₁ in persons without asthma who were participants in the third National Health and Nutrition Examination Survey (NHANES III) and were matched to our study participants for sex, race or ethnic group, age, and height at each spirometric session. Panel A shows the average FEV₁ trajectory for participants classified as having normal lung-function growth without an early decline (170 participants), Panel B shows the trajectory for participants who had reduced growth without an early decline (160 participants), Panel C shows the trajectory for participants with normal growth and an early decline (178 participants), and Panel D shows the trajectory for participants who had reduced growth and an early decline (176 participants).

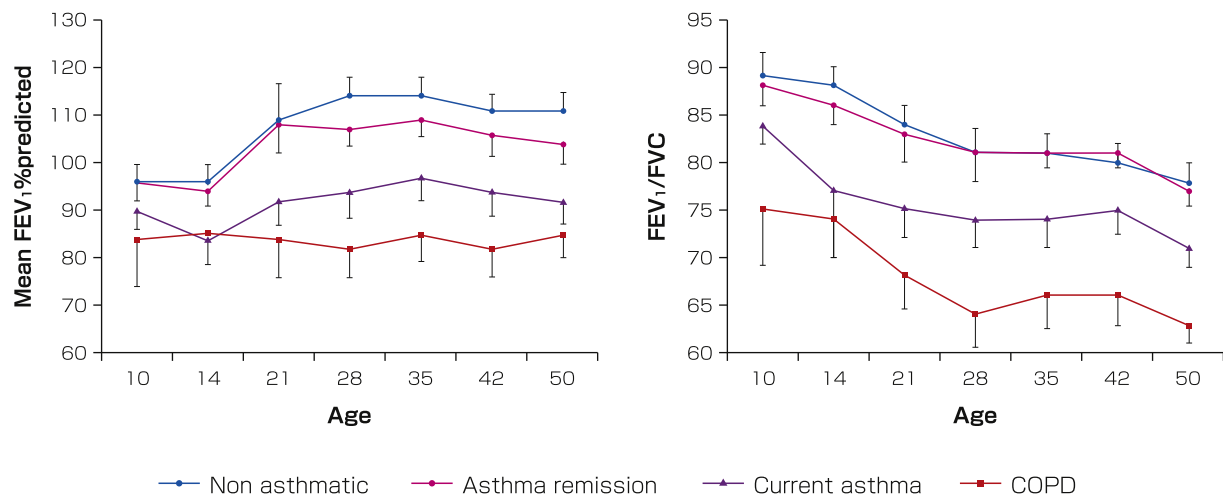


Fig. 9. Trend in mean FEV₁ per cent predicted and FEV₁ to FVC ratio over time (95th CI).

promoted airway hyperreactivity, male, and young age at the time of participation in the study.

e) Asthma status during early childhood and prognosis

The asthma status of children aged 6–7 years was classified into mild wheezy bronchitis, wheezy bronchiolitis, asthma, or severe asthma and their respiratory function was surveyed every seven years until they reached the age of 50 (Melbourne Asthma Cohort). Their status at the age of 50 was classified as non-asthmatic, asthma remission, current asthma, or COPD, and the relation between this status and their respiratory course from early childhood was investigated (Fig. 9).²⁶ The results indicated that at the age of 50, approximately 50% of the subjects classified as mild wheezy bronchitis or wheezy bronchiolitis were remitted, but 44% of the subjects classified as severe asthma were diagnosed with COPD.

(2) Reduced pulmonary function in late adulthood

After airway and lung growth and function reach a peak at around the age of 22, respiratory function starts to gradually decline. The factors that influence reduced pulmonary/respiratory function in cases of smaller than normal lungs that eventually reached normal growth are shown in Table 1. The degree of reduction in function affects the progression to airway obstruction (FEV_{1.0} < 70%) in cases of both normal growth and reduced growth.

As can be seen from the above, lung growth from the fetal stage particularly until the age of 5 years and the environment during early childhood have a strong relation to the formation of asthma and COPD pathophysiology. Thus, the mother herself and the environment during early childhood have an extremely important effect on lung growth. In addition, genes that are associated with lung growth, such as *HHIP* and *SOX5*, are known to be disease susceptibility genes for COPD, and epigenetic changes due to the environmental factors of other genes that regulate lung growth are also thought to be involved.

The course of overlap

In general, there are cases of asthma in which COPD overlaps – e.g. “cases with a history of asthma or currently diagnosed with asthma that have a history of smoking or currently smoke and present chronic and gradual progressive shortness of breath during exertion as well as chronic coughing and phlegm” – and cases of COPD in which asthma overlaps – e.g. “cases with a history of smoking or current smokers that become sensitized to an inhalation antigen and develop asthma.” As mentioned above, early childhood asthma is a cause of reduced lung growth and function

due to its effect on lung growth, and in such cases there is a likelihood that the individual will develop a pathophysiology that has features of both asthma and COPD. These, therefore, are issues that require careful attention in cases that develop the pathophysiology of ACO.

Conclusion

Epidemiological and clinical research continues to elucidate the pathophysiology and clinical features of asthma and COPD overlap. However, a large number of studies do not use a common definition and are not based on common diagnostic criteria for asthma, COPD, and ACO. In addition, many cases are undergoing treatment. ACO is a disease which has both features of asthma and COPD. While remodelled asthma, COPD and ACO are diagnosed from among cases of chronic obstructive airway disease that present an FEV₁ of under 70% after administration of fast-acting β_2 agonist after differentiated from other diseases, when making such diagnoses, it is important to understand the pathophysiology of ACO.

Conflict of interest

SH has received lecture fee from Kyorin, Nippon Boehringer-Ingelheim, AstraZeneca, Novartis, Astellas and GlaxoSmithKline, and research funding from Philips Respironics and Chugai. YG has received lecture fee from Nippon Boehringer-Ingelheim and AstraZeneca. MH has no conflict of interest.

References

1. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. Updated 2017. Available from: <http://www.ginasthma.org>.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *2017 Global Strategy for Prevention, Diagnosis and Management of COPD*. Available from: <http://goldcopd.org>.
3. Diagnosis of Disease of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS) 2014. Available from: <http://www.ginasthma.org/> or <http://goldcopd.org>.
4. American Thoracic Society. *Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease*. *Am J Respir Crit Care Med* 1995;152:S77–120.
5. Orie NGM, Sluiter HJ, De Vries K, Tammeling GJ, Witkop J. The host factor in bronchitis. In: Orie NGM, Sluiter HJ, editors. *Bronchitis*. Assen, The Netherlands: Royal Van Gorcum; 1961. p. 43–59.
6. Orie NGM, van der Lende R, editors. *Bronchitis III: Third International Symposium on Bronchitis*. Assen, The Netherlands: Royal van Gorcum; 1970. p. 115.
7. Xuan W, Peat JK, Toelle BG, Marks GB, Berry G, Woolcock AJ. Lung function growth and its relation to airway hyperresponsiveness and recent wheeze results from a longitudinal population study. *Am J Respir Crit Care Med* 2000;161:1820–4.

8. van den Berge M, Vonk JM, Gosman M, Lapperre TS, Snoeck-Stroband JB, Sterk PJ, et al. Clinical and inflammatory determinants of bronchial hyper-responsiveness in COPD. *Eur Respir J* 2012;**40**:1098–105.
10. De Marco R, Accordini S, Marcon A, Cerveri I, Antó JM, Gislason T, et al. Risk factors for chronic obstructive pulmonary disease in a Europe cohort of young adults. *Am J Respir Crit Care Med* 2011;**183**:891–7.
11. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011;**242**:10–30.
12. Van Eerdedewegh P, Little RD, Dupuis J. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002;**418**:426–30.
13. Jongepier H, Boezen HM, Dijkstra A, Howard TD, Vonk JM, Koppelman GH, et al. Polymorphisms of the ADAM33 gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy* 2004;**34**:757–60.
14. Gosman MM, Boezen HM, van Diemen CC, Snoeck-Stroband JB, Lapperre TS, Hiemstra PS, et al. A disintegrin and metalloprotease 33 and chronic obstructive pulmonary disease pathophysiology. *Thorax* 2007;**62**:242–7.
15. Cao SS, Kaufman RJ. Unfolded protein response. *Curr Biol* 2012;**22**:R622–6.
16. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;**448**:470–3.
18. Alcorn JF, Crowe CR, Kolls JK. TH17 cells in asthma and COPD. *Annu Rev Physiol* 2010;**72**:495–516.
19. Calışkan M, Bochkov YA, Kreiner-Møller E, Bønnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;**368**:1398–407.
20. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect of respiratory health and disease. *Lancet Respir Med* 2013;**1**:728–42.
21. Postma D, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet* 2015;**385**:899–909.
22. Morales E, Garcia-Esteban R, de la Cruz OA, Basterrechea M, Lertxundi A, de Dicastillo MD, et al. Intrauterine and early exposure to outdoor air pollution and lung function at preschool age. *Thorax* 2015;**70**:64–73.
23. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;**65**:14–20.
24. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;**370**:758–64.
25. McGeachie MJ, Yate KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Pattern of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;**374**:1842–52.
26. Tai A, Tran H, Robert M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;**69**:805–10.