



ERS | *monograph*

Respiratory Epidemiology

Edited by
Isabella Annesi-Maesano,
Bo Lundbäck and
Giovanni Viegi

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Editor in Chief
Tobias Welte

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Tobias Welte, Editor in Chief

Pulmonary diseases affect millions of patients every year worldwide. COPD, asthma and allergies are among the most widespread, affecting more than 5% of the total population. Diseases induced by cigarette smoke, such as chronic bronchitis, COPD and lung cancer, can be avoided, but intense social and political engagement is required in order for disease prevention programmes to succeed.

Research into the pathophysiology and genetics of pulmonary diseases has increased greatly in the last decade. This has led to new developments in lung cancer treatment and new therapies for asthma; in addition, COPD and interstitial lung fibrosis have been evaluated and are now included in treatment guidelines. The level of development in this area of respiratory medicine is highlighted by the establishment of the first causal therapy for cystic fibrosis with genetic modifiers, and the improvement in long-term prognosis in pulmonary hypertension patients using a combination of various drugs.

In the past, treatment of respiratory conditions took place outside the major cities, mainly because TB was one of the major diseases. Pneumology was therefore only marginal a part of internal medicine. Fortunately, this has gradually changed over the years, in some countries more than others. Today, pneumology is almost at the centre of internal medicine. This opens new fields of interest where respiratory medicine overlaps with many other disciplines. Some of the most important areas of overlap are: oncology in the field of thoracic neoplasms; cardiology for pulmonary hypertension; infectious diseases connected with pneumonia and TB; intensive care for patients with respiratory failure and the severely ill; dermatologists and ear, nose and throat specialists in allergology; neurologists and psychiatrists in sleep medicine; and geriatricians and palliative care physicians involved in the care of patients with terminal illnesses.

This issue of the *ERS Monograph* demonstrates the development of respiratory medicine convincingly. It provides an overview of



the essential epidemiological figures for all who work in respiratory diseases. It should also be used to increase the visibility of respiratory medicine, and could serve as a basis in political negotiations about the need for increasing budgets for respiratory medicine.

I want to congratulate the Guest Editors Isabella Annesi-Maesano, Bo Lundbäck and Giovanni Viegi for their tremendous work in setting up this important *Monograph*. I am convinced that readers will find it useful in their daily work.



Guest Editors

Isabella Annesi-Maesano

Isabella Annesi-Maesano is the NIH Research Director and Professor of Environmental Epidemiology at the Universities Pierre and Marie Curie (UPMC) and René Descartes (both Paris, France), and Director of the Dept of Epidemiology of Allergic and Respiratory Diseases (EPAR) (www.epar.fr) at the Institute Pierre Louis of Epidemiology and Public Health of the French NIH and the UPMC in Paris. In 2013, she was appointed as a member of the Directoire at the Observatory for the Sciences of the Universe “Ecce Terra” at UPMC. She is an active member of several professional societies, including the European Respiratory Society (ERS), the American Thoracic Society (ATS), the European Academy of Allergology and Clinical Immunology (EAACI) and the International Society for Environmental Epidemiology (ISEE). She is currently a member of the ERS Environmental and Health Committee, and Chair of the EAACI Interest Group Aerobiology and Air Pollution. She previously served as a member of the ERS Executive Committee, Chair and Secretary of the Occupation and Epidemiology Assembly, and Chair and Programme Secretary of the Respiratory Diseases section of the International Union Against Tuberculosis and Lung Disease. She serves on several editorial boards, including the *European Respiratory Journal*, the *European Respiratory Review* and *Allergy*.



Isabella Annesi-Maesano was trained as a respiratory epidemiologist after a double curriculum in physics and medicine, and a PhD in epidemiology and biostatistics. Her personal research interest focuses on the distribution and aetiology of asthma, COPD, interstitial pulmonary diseases and rhinitis using an exposomic approach (the internal and external environmental stressors an individual encounters in their lifespan, particularly their early life), and identifying phenotypes/endotypes. Her research has been funded by the French Ministries of Health, Research, and Environment and Sustainable Development, the French Environmental Agency (ANSES), the European Commission, and others. Since 2013, she has coordinated the interdisciplinary translational research project HEALS (Health and Environment-wide Associations based on Large population Surveys) part of the

FP7-ENV (7th Framework Programme for EU Research: Environment) programme, integrating clinics, epidemiology, toxicology, omics, sociology and other disciplines to advance understanding about respiratory diseases through exposomics. The study is recruiting new birth cohorts of singletons and monozygotic and dizygotic twins in Europe that will be followed over a course of time. She has more than 300 papers and chapters in peer-reviewed journals and books. She collaborates with 30 international institutions.

Giovanni Viegi



Giovanni Viegi is acting Director of the CNR Institute of Biomedicine and Molecular Immunology (Palermo, Italy), leader of the Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology (Pisa, Italy), and Contract Professor at the Faculty of Environmental Sciences of the University of Pisa. He graduated in Medicine *magna cum laude* and specialised in pulmonology and occupational medicine.

Giovanni Viegi is a member of the Executive Committee of the Italian Society of Respiratory Medicine (SIMeR), Past President of the European Respiratory Society (ERS), the Italian representative for the Global Alliance against Chronic Respiratory Diseases (GARD), and is a member of the American Thoracic Society (ATS) and the International Union Against Tuberculosis and Lung Disease (IUATLD). From 1998 to 2001 he was a member of “Technical-scientific Committee for elaboration of law proposals in the matter of indoor pollution” at the Italian Ministry of Health.

Giovanni Viegi’s main research interests and areas of grant coordination are: lung function assessment; the epidemiology of COPD in relation to air pollution; respiratory occupational medicine; respiratory allergology; the epidemiology of cardio-respiratory and psychiatric comorbidity; and clinically controlled smoking cessation.

With the Pisa research group, he has conducted the two largest respiratory epidemiological longitudinal studies on general population samples in Italy (in the Po Delta and Pisa areas).

Giovanni Viegi serves on the editorial boards of the *Medicina Respiratoria*, the official journal of the Asociación Argentina de Medicina Respiratoria, and the *Rassegna di Patologia dell’Apparato Respiratorio*, the official Journal of the Associazione Italiana Pneumologi Ospedalieri (AIPO). He is the author of 299 original articles (198 in English), 56 book chapters (19 in English) and 140 proceedings (49 in English).

Bo Lundbäck

Bo Lundbäck is Professor of Respiratory Epidemiology at the Institute of Medicine/Krefting Research Centre at the University of Gothenburg (Gothenburg, Sweden). He is affiliated with the Dept of Respiratory Medicine and Allergy at the Institute of Public Health and Clinical Medicine University of Umeå (Umeå, Sweden), and the Dept of Research and Development at the County Council of Norrbotten (Luleå, Sweden).

Bo Lundbäck is currently the Head of the Occupation and Epidemiology Assembly of the European Respiratory Society (ERS) and a member of the Society's Executive Committee, Science Council, Environment and Health Committee, and Tobacco Control Committee. He is Associate Editor of *Respiratory Medicine* and a member of the editorial board of the *Journal of Chronic Obstructive Pulmonary Disease* and the *European Clinical Respiratory Journal*. He was one of the editors of the *The European Lung White Book*, second edition.

Bo Lundbäck's research mainly focuses on clinical respiratory epidemiology and he has been the scientific leader of several large-scale epidemiological and clinical studies, as well as health economics studies. The main studies in which he has been involved include: the Obstructive Lung Disease in Northern Sweden (OLIN) Studies, which have been in progress since 1985 with more than 50 000 participants; and the FinEsS Studies, which compare the epidemiology of asthma, allergy, COPD and respiratory symptoms in Finland, Estonia and Sweden. He is co-chair of the West Sweden Asthma Study, which covers epidemiology, clinical research, and research on cellular mechanisms, including proteomics and genetics.

He has supervised more than 20 PhD students from several countries, including Sweden, Finland, the USA, Estonia and Vietnam, and has collaborated closely with several universities and hospitals in Europe and worldwide, from the University of Virginia (Charlottesville, VA, USA) in the west to Hanoi Medical University (Hanoi, Vietnam) in the east. He has more than 170 publications on PubMed.





Introduction

Isabella Annesi-Maesano^{1,2}, Bo Lundbäck³ and Giovanni Viegi^{4,5}

Fifteen years ago, officers of the Occupation and Epidemiology Assembly of the European Respiratory Society (ERS) had the idea of disseminating the concepts and results of the respiratory epidemiological studies carried out in Europe to the membership of the ERS. Thus, in the year 2000 the Respiratory Epidemiology in Europe issue of the *ERS Monograph*, edited by Isabella Annesi-Maesano, Amund Gulsvik and Giovanni Viegi, was published [1]. It covered a broad spectrum of topics, including COPD, study design, and environmental and behavioural risk factors. In all, there were 21 chapters: seven were methodological, five were devoted to specific diseases, and nine dealt with risk factors. The book helped generate an understanding of the importance of epidemiology as a basic component of medical culture, and was an important advocacy tool. Indeed, a few years later, the ERS and the European Lung Foundation (ELF) published the first edition of the *European Lung White Book* [2], which was instrumental to the ERS' success in convincing the European Commission (EC) of the need for including respiratory and allergic diseases amongst the diseases for which funding was planned in FP7 (7th Framework Programme for EU Research) [3]. Last year, the ERS published the new version of *The European Lung White Book* [4], an updated advocacy tool that will generate more attention and research funding for respiratory medicine.

Respiratory epidemiology has greatly advanced in last 15 years. It has allowed us to fill gaps in the knowledge about major respiratory diseases and to investigate them further. It is now time to launch the updated edition of the Respiratory Epidemiology *ERS Monograph*.

This update of the *Monograph* considers the advances that have been accomplished by respiratory epidemiology in contributing to a better understanding of respiratory health and disease prevention. The updated version covers a broader spectrum of topics than the first version and includes 21 chapters: seven are devoted to the most commonly encountered respiratory diseases, 10 consider risk factors, two focus on methodology, and two discuss the economic burden of major respiratory diseases. In a changing world, the updated *Monograph* addresses new or poorly treated issues at the population level, such as poverty, air pollution (a growing burden due to climate change), rhinitis, interstitial lung diseases and obstructive sleep apnoea (which are increasing in prevalence), and also covers epigenetic–environment interactions when appropriate.

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Most of the authors are members of the Occupation and Epidemiology Assembly of the ERS. The Assembly is active in developing epidemiology and several leading persons from large-scale local and international studies, as well as research consortiums, such as ECRHS (European Community Respiratory Health Survey), ISAAC (International Study of Asthma and Allergies in Childhood), GA²LEN (Global Allergy and Asthma European Network), BOLD (Burden of Obstructive Lung Disease) and GOLD (Global Initiative for Chronic Obstructive Lung Disease), are members of the Assembly. The work of the Assembly increases knowledge about environmental, occupational and lifestyle factors, such as the risks of developing respiratory diseases, and also considers factors that contribute to respiratory health [5]. The Epidemiology Group and the Occupational and Environmental Health Group are deeply involved in these studies. Special interest is paid, among others, to the most important single risk factor for respiratory disease, smoking, and the work of the Tobacco, Smoking Control and Health Education Group focuses on the severe and hazardous effects of active and passive smoking. As a result of the increase in understanding about the importance of the interaction of genes and the environment, a fourth Group, Genes and Environment, recently started activities.

One of the most important tasks of the Occupation and Epidemiology Assembly is advocacy. During the presidency of Giovanni Viegi two important advocacy committees were established: the Tobacco Control Committee (TCC) and the Environment and Health Committee (EHC). The TCC was preceded by the Smoking Prevention Committee, established in 1998. The committees work closely with the ERS Brussels office, the ERS Headquarters and the ELF in lobbying for respiratory health in Europe, and worldwide *via* the World Health Organization (WHO). The Assembly collaborated with WHO in the foundation and management of the Global Alliance against Chronic Respiratory Diseases (GARD). Both committees organise evening sessions at the European Parliament and informative activities for the EC. Another example of the committees' activities was the EHC initiative to organise the first international conference held by a respiratory society on the health effects of climate change [6].

The Assembly has organised several conferences and task forces, and has produced *Monographs* and important position papers, among them position papers on the respiratory effects of air pollution and occupation [7, 8]. Recent task force reports include updated recommendations on epidemiological studies of COPD [9] and occupational asthma [10]. Members of the Assembly were also part of the Editorial Boards of both the first and the second editions of the *European Lung White Book* [2, 4].

Perspectives

It is important that healthcare providers and society as a whole know about the prevalence and trends of prevalence and incidence of major disease, including the respiratory diseases. Large-scale population studies are necessary for the calculation of prevalence of, for example, COPD and asthma. Information from registry data is not enough to calculate the prevalence of COPD in society, as under-diagnosis is huge; large-scale epidemiological studies that include spirometry are required. The diagnosis of asthma is arbitrary, and irrespective of international guidelines, asthma has in reality been classified differently in many parts of the world, including Europe. Thus, population studies also provide important information about asthma, and international studies allow comparison of prevalence between areas and countries.

Prevalence studies, *i.e.* cross-sectional studies, may provide data about risk factors for diseases; however, a found association could be a cause, a consequence of disease or a parallel phenomenon. Thus, longitudinal studies of cohorts of the general population are needed as these studies provide more valid results regarding risks, and the probability of the associations being risks is greater than that of the associations that are derived from cross-sectional studies. These important methodological aspects have been explored in a chapter of this *Monograph*.

One important area that requires consideration is rare respiratory disease. In Europe, a disease or disorder is defined as rare when it affects less than one in 2000 people; however, as many as 30 million people may be affected by one of over 6000 rare diseases. It has been shown that many major diseases can be subdivided into individual diseases called phenotypes, some of which are classified as rare. This is often the case with respiratory disease. Rare diseases constitute appropriate models for the underlying mechanisms of other diseases. The specific features associated with rare diseases (low individual patient numbers, diversity, geographical location) mean that research needs to be developed at a large level in order to optimise funding, infrastructures and technological platforms. Patient registries and databases are key to the development of epidemiological and/or clinical research in this area, as they pool data and achieve a sufficient sample size, leading to improvements in patient care and healthcare planning. The creation of a rare respiratory disease registry would also be a powerful tool in creating a network of experts.

Due to the increasing difficulty and cost of carrying out new general population surveys, in which a progressively decreasing proportion of people agree to participate, it is likely that there will be rise in the epidemiological use of routinely collected statistics, as well as medical records stored by family practitioners. Data mining procedures within the huge database created by the widespread use of e-health instruments (patient diaries, electronic health cards, *etc.*) will help.

Another important issue that needs to be developed in the future is exposomics. Genetics have been found to account for only around 10% of diseases, and the remaining causes appear to be environmental. In order to understand the causes of respiratory disease and its prevention, the impact of the environment needs to be further investigated. Exposomics can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to his/her health. In respiratory disease, an individual's exposure begins before birth with passive smoking and includes insults from the environment, like air pollution, diet, lifestyle and occupational sources, and their interactions with characteristics such as genetics, epigenetics and physiology. This requires appropriate methodologies, such as epidemiology, biostatistics, omics and data mining.

Respiratory epidemiology also plays an important role in translational research, and molecular epidemiology is increasingly important. Modern translational research covers epidemiology, clinical aspects (including phenotyping or endotyping) and research on cellular mechanism (including inflammation, proteomics and genetics). The contribution of epidemiology can guarantee a representative sample for study. Studies of the gene-environment interaction play an increasing role in modern epidemiological research.

We believe that in this issue of the *Monograph* the reader will find methodological information and content that will be useful in forthcoming calls for research proposals issued by the EC within the framework of Horizon 2020, which includes relevant themes for public health and respiratory medicine.

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List of abbreviations

AIDS	Acquired immune deficiency syndrome
ALRI	Acute lower respiratory infection
ARDS	Acute respiratory distress syndrome
BCG	Bacilli Calmette–Guerin
BHR	Bronchial hyperresponsiveness
BMI	Body mass index
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DALY	Disability-adjusted life years
DLCO	Diffusing capacity of the lung for carbon monoxide
FeNO	Exhaled nitric oxide fraction
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
ICU	Intensive care unit
Ig	Immunoglobulin
IL	Interleukin
IQR	Interquartile range
LRTI	Lower respiratory tract infection
NSCLC	Nonsmall cell lung cancer
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
PEF	Peak expiratory flow
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SDB	Sleep-disordered breathing
TB	Tuberculosis
TNF	Tumour necrosis factor