







Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration

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The ERS launches a new Clinical Research Collaboration (CADSET) to study the determinants and implications of different lung function trajectories through life <http://ow.ly/nf4E30nGsJG>

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Introduction

A recent editorial in the *European Respiratory Journal* highlighted the strategic importance of the Clinical Research Collaborations (CRCs) launched in 2013 by the European Respiratory Society (ERS) [1]. These have the aim of 1) promoting the exchange of research ideas among clinicians and affiliated scientists in Europe and/or globally; 2) building an infrastructure for prospective clinical research; 3) securing additional funding through national and European Union funding streams; and 4) facilitating the planning, implementation, evaluation and publication of clinical and translational studies at pan-European level and beyond. So far, there are currently 17 ongoing CRCs that cover eight major respiratory disease domains (airway diseases, interstitial lung diseases, pulmonary vascular diseases, sleep and breathing disorders, respiratory critical care, paediatric respiratory diseases, respiratory infections and thoracic

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oncology), all of them linked to one or more ERS assemblies [2–12]. CADSET, an acronym that stands for “Chronic Airway Diseases Early Stratification”, is the latest addition to the list of ongoing CRCs (www.ersnet.org/research/clinical-research-collaborations). This editorial presents the rationale, goals and research strategy for CADSET.

Scientific rationale

Asthma and chronic obstructive pulmonary disease (COPD) are the two most prevalent chronic respiratory diseases and neither has a curative therapy [13, 14]. A third of the population will develop asthma at some point in their lives [13], and COPD affects 10% of the adult population, currently being the third leading cause of noncommunicable deaths globally [15]. Both asthma and COPD are complex and heterogeneous diseases, and their differential diagnosis is often not straightforward [16–20]. Indeed, it is suggested that asthma and COPD might actually represent a continuum of chronic airway diseases with shared clinical, functional, imaging and/or biological features [21]. However, asthma is still considered a disease of infancy or early adulthood, often related to some form of allergy [22], whereas COPD has been traditionally considered a disease of late adulthood, induced by smoking, and generally associated with an accelerated decline in lung function with age [23]. As a result, asthma is the most likely diagnosis that a child, adolescent or young adult will receive if they complain of respiratory symptoms, whereas a COPD diagnosis would be most likely in an older male smoker presenting with similar respiratory symptoms.

By contrast, recent evidence argues that there is an important role for abnormal lung development *in utero* or after birth in the pathogenesis of both asthma and COPD [24–30]. It is very likely that abnormal lung development and accelerated lung function decline (which also occurs in asthma) are associated with different biological mechanisms (*i.e.* endotypes), requiring different therapeutic interventions [18]. Of note, some children with impaired lung function early in life may exhibit “lung function catch-up” before adulthood (figure 1) [31–40], although the precise factors and mechanisms involved are currently unknown. A better understanding of the pathophysiology of this “catch-up” (or its absence) may prove extremely important in helping us to optimise lung growth, discern the reasons why particular individuals develop disease and, eventually, provide a novel therapeutic approach in adults with COPD [41, 42]. In any case, the available evidence indicates that to better understand the pathobiology of asthma and COPD, increase the specificity of their diagnosis and improve both the efficacy and safety of their treatment, we need to adopt a better understanding of the lung function trajectory of the patient throughout life (figure 1) [41].

Working hypothesis

From the aforementioned evidence, CADSET hypothesises that a multilevel (clinical, functional, imaging and molecular) profiling of well-characterised patients with chronic airways disease spanning the spectrum of asthma and COPD, which considers both peak lung function achieved in early adulthood and the rate of lung function decline, may lead to the identification of distinct mechanisms (endotypes) and appropriate biomarkers. These biomarkers may in turn inform a mechanism-based disease classification,

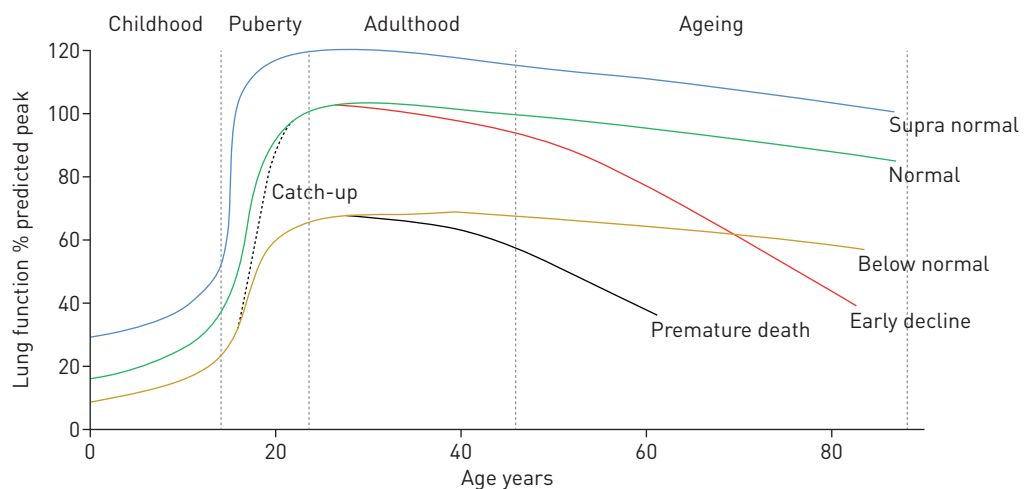


FIGURE 1 Schematic representation of different potential lung function trajectories through life. The term “catch-up” refers to the potential lung function recovery that may occur (for still unclear reasons) in some children. Reproduced and modified from [41] with permission.

identify interventional targets and thus favour a more personalised treatment of patients with chronic airways diseases.

Objectives

The strategic objective of CADSET is to create a consortium in which investigators with access to population cohorts, birth cohorts and cohorts of patients with asthma or COPD can work together to better understand how lung function trajectories influence the clinical presentation of chronic airway diseases, asthma and COPD in particular. A second important strategic objective of CADSET is to help young investigators to develop their academic careers, as reflected by their management role as work package leaders in CADSET.

The specific objectives of CADSET are: 1) to provide a multicentre, multidisciplinary platform to investigate lung function trajectories on the clinical presentation of chronic airway diseases; 2) to create a registry of currently available cohorts (and associated metadata and/or existing biobanks) in order to launch joint meta-analyses and targeted laboratory studies; 3) to share expertise and resources, creating common research protocols in order to enable the comparison and integration of data across different types of cohorts; 4) to promote the exchange of research ideas among participants; 5) to find distinct biological mechanisms and endotypes, and associated biomarkers, that identify underlying different lung function trajectories in order to move COPD and asthma assessment and therapy towards a precision medicine framework; and 6) to gain eligibility for public and private funding.

Research strategy

Under the auspices of the ERS, CADSET is based on a collaborative partnership model between the different stakeholder groups, *e.g.* clinician researchers, scientific experts, funding partners and patient advisors, where the project proposals and results are openly discussed. The collaboration of all stakeholders aims to drive the research strategy of CADSET, which is organised on the basis of five different working groups (WGs), each of them with a clear focus.

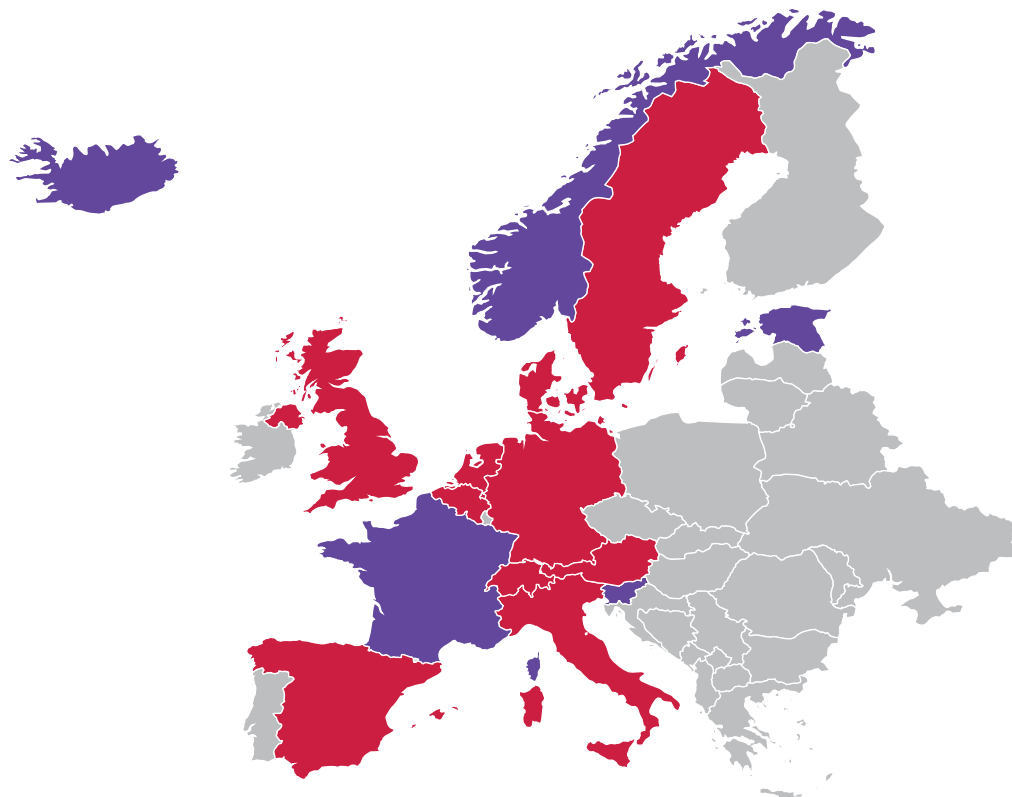


FIGURE 2 Cohorts and research groups currently participating in the Chronic Airway Diseases Early Stratification (CADSET) Clinical Research Collaboration. Red indicates countries with available cohorts and investigators, whereas purple indicates countries with available cohorts but not investigators (yet).

WG1: Registry

WG1 aims to develop a registry of sharable consortium resources on existing cohorts (including environmental, clinical, physiological, 'omic and imaging data, and biobanked blood, sputum and tissue samples) and to collate and share best practices from research protocols and standard operating procedures. The aim of WG1 is not to physically centralise data and samples in a single place but to assess the feasibility of assembling such resources for further studies as identified in the other WGs, and for commissioned projects from external groups and industry partners. So far, 33 cohorts have been registered and are available in the CADSET registry (figure 2). Data and sample sharing will always require the respective cohort principal investigators and governance committee agreement and be undertaken according to the General Data Protection Regulation.

WG2: From conception to age 25 years

WG2 will investigate the phenotypes and endotypes of suboptimal peak lung function at early adulthood (aged <25 years). In particular, it will first investigate the existence of different early life lung function trajectories (e.g. linked to early bronchial obstruction ("asthma"), wheezing or symptoms due to other conditions, or suboptimal lung development) and the mechanisms underlying potential lung function catch-up [36, 41]. Stratified analyses according to sex will be performed (since females obtain their peak lung function at an earlier age than males [43]).

WG3: From age 25 to 50 years

WG3 will investigate the clinical and underlying biological heterogeneity and related biomarkers of lung function decline in early adulthood. This will focus particularly in relation to the presence and severity of emphysema, chronic mucus hypersecretion, concomitant asthma, eosinophilic inflammation, concomitant comorbidity and response to specific pharmacological treatment (precision medicine [44]). As in WG2, stratified analyses according to sex will be performed [43].

WG4: From age 50 years onwards

WG4 will integrate multilevel data such as genetics, genomics, methylation and proteomics on similar biological samples from well-defined populations with "asthma" or "COPD" in order to understand molecular phenotypes that may be common or distinct to chronic airway diseases in this age range. This will be linked to readily accessible physiological, blood or breath biomarkers.

WG5: Understanding life-long lung function trajectories

The long-term goal of WG5 is to integrate the age-related results of WG2, WG3 and WG4, so that the strategic goals of CADSET can be fulfilled. CADSET will collaborate with other established CRCs, such as SHARP (The Severe Heterogeneous Asthma Research collaboration, Patient-centred) [5] and the Global Lung Function Initiative (GLI) network [10].

Support and participation

As for the other CRCs, the ERS provides some economic support, mainly to allow the organisation of face-to-face meetings, such as the one held in Barcelona, Spain, in December 2018. Besides this, the ERS acts as an independent broker between industry and the academic researchers. It is hoped that several companies may be interested in supporting CADSET financially. Likewise, it is envisaged that CADSET investigators will be able to raise additional funds from national and international competitive calls.

If you want or can contribute to CADSET with a cohort that helps in achieving the objectives outlined here, please contact the WG members or the ERS through the CADSET webpage (www.ersnet.org/research/cadset-chronic-airway-diseases-early-stratification).

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Current members of the CADSET Clinical Research Collaboration are as follows. Co-chairs and WG5 co-leaders: Alvar Agusti and Jadwiga A. Wedzicha. WG1 co-leaders: Gavin Donaldson, Rosa Faner and Robab Breyer-Kohansal. WG2 co-leaders: Anke H. Maitland-van der Zee and Erik Melén. WG3 co-leaders: James P. Allinson, Lowie E.G.W. Vanfleteren and Jørgen Vestbo. WG4 co-leaders: Ian M. Adcock, Lies Lahousse and Maarten van den Berge. Additional CADSET members: Peter Alter, Ferran Barbe, Christopher E. Brightling, Marie-Kathrin Breyer, Otto C. Burghuber, Maribel Casas, Kian Fan Chung, Borja G. Cosío, Fatima Crispi, Jordi de Batlle, Jean-William Fitting, Judith Garcia, Jenny Hallberg, Sylvia Hartl, Deborah Jarvis, Alexander Mathioudakis, Laurent Nicod, Alberto Papi, Andrew Ritchie, Torben Sigsgaard, Peter J. Sterk, Anders Ullman, Kilian Vellvé, Claus Vogelmeier, Asa M. Wheelock, Craig E. Wheelock and Antonio Spanevello.

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