

TITRE DU CONSORTIUM :

CONSTANCESRespi - Surveillance, determinants, natural history and impact of chronic respiratory diseases and accelerated lung function decline in CONSTANCES - An Integrative project

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PRESENTATION OF THE CONSORTIUM

Background

Asthma and COPD represent the most frequent non-communicable chronic respiratory diseases, with a high burden in terms of morbidity, mortality and direct and indirect expenses. Their burden is steadily increasing, as reflected by, e.g., the rise in COPD-related mortality and the increase in asthma prevalence. Few incidence data are available in France, and international studies provide limited information in middle-aged and older adults. Under-diagnosis is a crucial and difficult issue, especially for COPD. Late diagnosis and delayed treatment may be responsible for increased costs.

Asthma is frequently associated with allergy, particularly in children and young adults, and the prevalence of allergy is also rising in many developed countries. Besides, non-allergic late-onset asthma is recognized as a specific phenotype of severe asthma.

Both asthma and COPD cover heterogeneous phenotypes, that are likely related to distinct causes, different underlying mechanisms and variable natural history. Current evidence suggests that present and future changes in the epidemiology of asthma and COPD relate at least in part to ageing, way of life including occupation, obesity, physical activity/inactivity, diet, other related environmental exposures, and gender and “hormonal” status.

For both asthma and COPD, several questions remain unanswered, notably regarding:

- Evolution of their incidence and prevalence over time in France.
- Prevalence of the overlap syndrome (patients presenting asthma + COPD), and the similarities and differences between asthma, asthma in smokers, COPD, COPD in non-smokers.
- Disease phenotypes, distribution, risk factors, their stability over time and their implications in terms of therapeutic strategy.
- The effect of age, gender, socioeconomic characteristics including occupation, atmospheric air pollution, domestic environment, physical activity, nutrition, obesity and adiposity as determinants or modulators of the disease occurrence, impact and history.
- The nature of the relationship between COPD, asthma and comorbid illnesses. More generally, the cross-talks between the respiratory tract and other organs (/microbiota /metabolism /immunity).

- How they affect social life and productivity at the population level.
- Their relationships with mental well-being /depression, and stress at work.
- Strong, easily accessible and reliable public health indicators of their burden.
- Biomarkers predictive of the disease history or response to treatments.

The “CONSTANCES Respiratory Consortium”

The Consortium comprises several French teams involved in research on the epidemiology of asthma and COPD, their causes, phenotypes and natural history. Most of these teams already share research projects on various aspects of these topics.

It was recognized that the CONSTANCES cohort offers a unique opportunity to build research projects aimed at answering the above-mentioned questions on the epidemiology of asthma and COPD, more specifically regarding diseases’ burden, etiologies and related phenotypes, interactions with comorbidities, influence of demographic, socioeconomic and environmental characteristics including occupational aspects.

Therefore, each participating team commissioned one researcher to be part of the Scientific Committee of the Constances Respiratory Consortium. The role of this Committee was to identify relevant unanswered questions, prioritize them and select those that would be part of the present submission.

All projects rely on a common set of variables, especially including spirometry. Some will need additional variables that are part of the general list of CONSTANCES’ recorded items. Finally, some will require recording specific variables that are not part of the pre-planned set of variables.

Objectives

The present global project includes 7 individual but interacting projects listed below.

- Project 1: Prevalence, determinants and Impact of chronic airflow limitation and accelerated lung function decline
- Project 2: Asthma only / COPD without asthma / Asthma with COPD (overlap syndrome). A comprehensive analysis
- Project 3: Surveillance of Chronic Respiratory Diseases
- Project 4: Surveillance of Chronic Respiratory Diseases in relation to work
- Project 5: Heterogeneity and etiology of asthma, rhinitis and COPD, with 4 components:
 - Blood inflammatory patterns and asthma/asthma control in the Constances cohort
 - Occupational exposures to cleaning agents and irritants and new-onset asthma and asthma control
 - Body composition and respiratory diseases in the Constances cohort
 - Air pollution and allergic/non allergic rhinitis in Constances
- Project 6: Association between obstructive lung disease and HIV: an exposed/unexposed study in two smoking populations
- Project 7: Burden of dyspnea in respiratory diseases vs non respiratory conditions: relationships with patient reported outcomes and physical activity

Methods

The present project involves 7 research teams. Almost all work packages involve at least two of these teams (see page 1 for description of teams participation to the proposed projects). The global project is coordinated by the dedicated CONSTANCES Respiratory Scientific Committee, which will (1) ensure coherence among methods of data treatment and analysis and (2) avoid redundancies. Regular meetings of the Scientific Committee will be organized to plan data extraction and analyzes.

Perspectives

The above-mentioned projects have been considered by the CONSTANCES respiratory scientific committee as top priorities for near-future research. Other projects will be submitted later on.

Résumés des projets du consortium

PREVALENCE, DETERMINANTS AND IMPACT OF CHRONIC AIRFLOW LIMITATION AND ACCELERATED LUNG FUNCTION DECLINE

RESPONSABLE: Nicolas Roche

Background. Few data are available on risk factors of lung function decline in the general population. Better knowledge of these factors should help targeting at-risk populations requiring more intensive detection, follow-up and care to prevent poor outcomes.

Objectives. The purpose of this study will be to assess (1) factors associated with abnormal lung function and rate of lung function decline in the CONSTANCES cohort, and (2) the relevance of lung function as a marker of health status. Analyses will focus on:

1. Possible risk factors: exposures to environmental hazards including tobacco smoke and occupational exposures, socio-economic characteristics, intrinsic factors including age and gender, and some selected genetic risk factors and biomarkers.
2. Possible consequences of lung function impairment regarding morbidity, comorbid illnesses, health-related quality of life and handicap, consumption of health care resources and indirect costs.

Methods. Questionnaire, spirometry and biological data from Constances will be used.

Normal values of FEV1, FVC and FEV1/FVC ratio will be determined using previously published equations and equations derived from the non-smoking asymptomatic fraction of the CONSTANCES population.

Spirometry will be used to identify airflow obstruction (as defined by $FEV1/FVC < 0.70$ or $<$ lower limit of normal, LLN) and probable restrictive patterns, as defined by $FVC < LLN$ with $FEV1/FVC > LLN$.

The severity airflow obstruction will be classified using FEV1, and the severity of restrictive patterns will be classified using FVC.

Analyses: A dual approach will be used, studying:

- Factors (risk factors and markers of impact on health status) associated with abnormal lung function (airflow obstruction or restrictive pattern and their severity) at baseline.
- Factors (risk factors and markers of impact on health status) associated with the rate of FEV1, FVC and FEV1/FVC decline (categorized using tertiles) and occurrence of airflow obstruction or restrictive pattern during follow-up.

Factors associated with $FEV1 < LLN$ without airflow obstruction nor restrictive pattern will also be studied.

Risk factors of interest will be intrinsic risk factors (age, gender, obesity), environmental hazards (active and passive smoking, occupation and occupational exposure to vapours, dust, gas or fumes, biomass combustion in the home, atmospheric air pollution), nutritional habits, socio-economic status, nutritional habits, stress and psychological status, level of physical activity.

Genomic and proteomic studies will be addressed in a future application.

Markers of health status of interest will be respiratory symptoms, selected comorbidities (cardiovascular diseases, osteoporosis, depression, lung cancer), Health-related quality of life, activity of daily living, handicap and limitations, missed working days, consumption of healthcare resources.

Muscle strength and cognitive functions will also be studied in elderly subjects.

Gender-related and age-related differences in the risk factors-adjusted prevalence, severity and impact of lung function impairment will also be studied.

Statistical methods: associations will be studied using:

- univariate analysis followed by multivariate models to determine which factors are independently associated with lung function variables and their evolution, and their respective weights as determinants of lung function.
- Factor analyses including principal component, multiple correspondence and cluster analyses.

Foreseen timetable

The first series of analyses (factors associated with abnormal lung function) will be performed when 50% of the planned sample size will have been recruited, then at the end of inclusions (last first visit). The second series of analyses (factors associated with the rate of lung function decline) will be performed at the end of 5-year, 10-year and 15-year follow up.

ASTHMA ONLY / COPD WITHOUT ASTHMA / ASTHMA WITH COPD (OVERLAP SYNDROME)

RESPONSABLE: Bénédicte Leynaert

Background

Asthma and COPD are both heterogeneous diseases, whereby different phenotypes are likely associated with different environmental and host determinants. Comorbidities are frequent in asthma and COPD. Patients who have both asthma and COPD (overlap syndrome) appear to have a more rapid disease progression, more co-morbidities and health care utilization, than those with either disease alone. However, the joint distribution of asthma and COPD, as well as risk factors and long-term outcomes of the asthma and COPD overlap syndrome have been little investigated in the general population. It is still an open question whether asthma and COPD overlap syndrome is the result of asthma that has progressed to fixed airflow obstruction or a peculiar phenotype. Further research is required to identify factors that may protect asthmatics against progression into COPD, and, more generally, to improve our comprehension of the links between these conditions.

Objectives

The general objective is to study the distribution, natural course, and factors associated with Asthma only/ COPD without asthma/ Asthma with COPD (overlap syndrome). We will (1) assess the joint distribution of asthma and COPD by age and gender, (2) investigate prognosis after 5 years, (3) assess the relationships between asthma/COPD and comorbidities, and associations with risk factors in a comprehensive analysis to identify possible underlying mechanisms/common pathways, and (4) investigate gender differences in association with risk factors, comorbidities, Quality of Life and prognosis and appraise possible gender differential diagnosis.

Methods

Asthma will be defined according to questionnaire. COPD will be defined according to spirometry. Participants will be considered into 4 groups (i) No Asthma, No COPD; (ii) Asthma, without COPD; (iii) COPD without Asthma, (iv) Asthma and COPD. Prevalence by age and gender, and association with co-morbidities and risk factors, will be investigated through cross-sectional analyses of data at inclusion. Prognosis of patients with asthma and/or COPD (and gender differences in prognosis), and temporal relationship between asthma COPD overlap syndrome and co-morbidities and risk factors will be investigated through longitudinal analyses, after 3 and 5 years of follow-up.

Perspectives

Understanding the natural history, risk factors, and pathways involved in these cases of overlapping diseases may have critical implications for their prevention and treatment. A comprehensive analysis of co-morbidities and risk factors associated with asthma only, COPD without asthma, and asthma with COPD shall improve our understanding of the diseases development and progression, and their determinants.

SURVEILLANCE OF CHRONIC RESPIRATORY DISEASES

RESPONSABLE : Marie Christine Delmas

Background

Data on prevalence of chronic respiratory diseases in French adults are rare. Regarding COPD, only two studies conducted in the beginning included lung function testing. The only data on incidence and natural history of asthma and COPD were provided by the European community health respiratory survey (ECRHS), but no specific data from the French participants have been published.

Objectives

The specific objectives of the project are : 1/ to assess the prevalence of COPD, the proportion of undiagnosed COPD, the prevalence and the control of asthma, and the prevalence of allergic sensitization in the French adult population according to demographic and socioeconomic characteristics; 2/ To assess the incidence of COPD and the progression of airflow obstruction in COPD patients according to demographic and socioeconomic characteristics; 3/ To assess the incidence and natural history of asthma according to demographic and socioeconomic characteristics; 4/ To assess the incidence of allergic sensitization

Methods

The study population will comprise all participants in the cohort, except for the estimation of prevalence and incidence of allergic sensitization (performed in a random sample of participants at inclusion) and the estimation of control of asthma (performed in a random sample of asthmatic patients at inclusion). All prevalence and incidence estimates (and confidence intervals) will take into account the sampling plan and nonresponse, which will make it possible to extrapolate the results to the entire French adult population.

Perspectives

The monitoring of chronic respiratory diseases will provide a factual basis from which policy-makers could appropriately set priorities, plan programs, and take actions to promote and protect the public's health.

SURVEILLANCE OF CHRONIC RESPIRATORY DISEASES IN RELATION TO WORK

RESPONSABLE: Y Iwatsubo

Background

Role of occupational factors in the occurrence of chronic respiratory diseases has been studied and review articles have estimated that the population attributable risk for occupational factors was 10 to 25% for asthma and 15% for COPD. These diseases can have adverse impact on the subjects' future job and financial status.

Objectives

The objectives of the project are: 1) to assess the prevalence of these diseases by employment status, industry, occupation and occupational exposures; 2) to assess the control of asthma in relation to occupational parameters; 3) to assess the incidence of these diseases in relation to occupational parameters; 4) to determine attributable risk of occupational parameters in the occurrence of these diseases; 5) to study socioeconomic and occupational outcomes related to these diseases.

Methods

The study population will comprise all participants in the cohort, except for the study of allergic sensitization (performed in a random sample of participants at inclusion) according to occupational parameters and the study of control of asthma according to occupational parameters (performed in a random sample of asthmatic patients at inclusion).

Prevalence and Incidence rates, weighted for sampling plan and nonresponse, will be studied according to the participants' occupational characteristics.

Occupational parameters comprise industry and occupation categories of the participants and data provided by existing job exposure matrices.

Perspectives

Data from epidemiological surveillance will contribute to the definition of occupational health policies aimed at reducing the number and/or the severity of the diseases due to occupational factors.

HETEROGENEITY AND ETIOLOGY OF ASTHMA, RHINITIS AND COPD

RESPONSABLE : Rachel Nadif

Background: The respiratory working group will develop projects on asthma, chronic obstructive pulmonary disease (COPD), and rhinitis. Asthma is a complex and heterogeneous multifactorial disorder, that affects between 5 and 10% of the adult population and has important impact on the quality of life. Rhinitis is a common worldwide respiratory disease that affects between 20 and 50% of the population, and could be a risk factor for asthma. COPD was the third most common cause of death worldwide in

2010, and it is increasingly recognized that COPD is just one of the component of multimorbidity in patients with COPD. In spite of much research effort, the risk factors for asthma, rhinitis and COPD remain largely unknown, and the role of environmental factors is pointed out.

Objectives: The general objective is to better understand the etiology and the heterogeneity of asthma, COPD and rhinitis. We defined four specific projects 1) to investigate the associations between blood inflammatory patterns and asthma/asthma control according to age (project leader: R. Nadif), 2) to evaluate associations between occupational exposures, especially to cleaning agents and irritants, and new-onset asthma (project leader: N. le Moual), 3) to better understand how body composition affects respiratory diseases (project leader: R. Varraso) and 4) to refine rhinitis definitions and phenotypes and to study associations between long term exposure to air pollution and rhinitis (project leader: B. Jacquemin).

Methods: Projects will focus on environmental risk factors with a strong impact in public health such as occupational exposures and air pollution. Associations between occupational exposures and asthma control and various asthma phenotypes such as Immunoglobulin E (IgE)-dependent/non-IgE-dependent asthma and neutrophilic asthma will be studied. A specific standardized questionnaire on rhinitis has been designed and sent to the first follow-up. The evaluation of several exposure models for air pollution is currently in discussion. The associations between obesity and fat mass with asthma, and the associations between body composition and lung function decline, and the incidence of COPD will be investigated. Several biological phenotypes throughout the causal chain between environmental factors and diseases will be considered to better understand rhinitis aetiology. Cross-sectional and longitudinal analyses will be performed to reach the objectives.

Perspectives: These projects are based on an interdisciplinary research based on complementary skills in biology, statistics, clinical, respiratory and environmental epidemiology within or out of the respiratory working group. Overall, the projects developed in the respiratory group will improve the characterization of the respiratory diseases, allowing a better understanding of their heterogeneity, aetiology and biological mechanisms.

ASSOCIATION ENTRE INFECTION PAR LE VIH ET SYNDROME OBSTRUCTIF: ETUDE
DE TYPE EXPOSES/NON EXPOSES DANS DEUX POPULATIONS DE FUMEURS.
ÉTUDE TRANSVERSALE ET APPARIEE DE SUJETS ISSUS DE L'ETUDE ANRS EP48
HIV CHEST ET DE LA COHORTE EN POPULATION GENERALE CONSTANCES

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RESPONSABLE : Alain Makinson

Contexte : Les données de prévalence de la BPCO chez les PVVIH sont restreintes à quelques études de comparaison de données américaines de morbidité basée sur l'information hospitalière entre une population exposée ou non à l'infection par le VIH. Ces études suggèrent une prévalence plus élevée de la BPCO au cours de l'infection par le VIH. Les facteurs de risques de la BPCO chez les PVVIH se divisent en facteurs de risque non spécifiques, identiques à ceux de la population générale et des facteurs de risque liés à un possible effet de l'infection par le VIH. En ce qui concerne les facteurs spécifiques à l'infection par le VIH, les données sont rares et incertaines. Des études comparatives entre des sujets issus de la population générale non exposés à l'infection par le VIH et des PVVIH sont nécessaires pour mieux appréhender les rôles respectifs de l'infection VIH et des autres facteurs de risque dans l'association avec la BPCO.

Objectifs

Principaux : 1) Comparer la prévalence du syndrome obstructif entre une population de PVVIH (groupe de sujets exposés) à haut risque de BPCO de par un tabagisme ≥ 20 paquets-années issue de l'étude ANRS EP48 HIV CHEST et une population de sujets non exposés au VIH issue de la cohorte en population générale CONSTANCES à risque identique de BPCO, après appariement sur l'âge et le genre. 2) Déterminer si l'infection par le VIH est un facteur associé indépendant au syndrome obstructif après ajustement sur les co-variables.

Secondaires : Comparer les valeurs du rapport VEMS/CVF entre les deux populations appariées sur l'âge et le genre.

Méthodes : Toutes les données des PVVIH sont issues de l'étude française multicentrique et prospective ANRS EP48 HIV CHEST. Les principaux critères d'inclusion étaient : 1) un nadir de lymphocytes TCD4 $< 350/\mu\text{l}$, 2) un taux de lymphocytes TCD4 à l'inclusion $> 100/\mu\text{l}$, 3) un tabagisme chronique ≥ 20 paquets-années, actif ou sevré depuis ≤ 3 ans, 4) et un âge ≥ 40 ans. Une étude ancillaire a évalué par spirométrie le VEMS et la CVF chez 353 sujets volontaires. La population non exposée à l'infection par le VIH sera issue de la cohorte CONSTANCES, des mêmes départements si possible ou régions que les CHU ayant participé à l'étude ancillaire de HIV-CHEST. Tous les sujets de la cohorte en population générale CONSTANCES seront des fumeurs de plus de 20 paquets-années. L'appariement sera d'une PVVIH avec trois sujets recrutés dans CONSTANCES sur l'âge et le genre.

Le critère de jugement principal est un syndrome obstructif défini par le rapport VEMS/CVF < 0.70 et une valeur du VEMS < 80 % de la valeur théorique. La comparaison du critère de jugement entre les deux populations sera réalisée à l'aide d'un modèle logistique à effets mixtes. Afin d'évaluer si le statut infection à VIH est indépendamment associé au syndrome obstructif, un modèle multivarié sera construit en incluant les co-variables d'ajustement choisis. Les interactions éventuelles entre le statut infection à VIH et les co-variables seront recherchées. L'association entre le rapport VEMS/CVF et le statut infection à VIH sera évalué par un modèle de régression linéaire à effets mixtes.

Perspectives : 1) Comparer la prévalence du syndrome obstructif dans ces deux populations 2) Évaluer le « poids » des variables non spécifiques des PVVIH et de l'infection par le VIH, dont certaines sont modifiables (tabagisme) et des interactions de ces variables avec le statut « infection par le VIH ».

DETERMINANTS AND BURDEN OF DYSPNEA IN RESPIRATORY DISEASES AND NON-RESPIRATORY CONDITIONS: RELATIONSHIPS WITH PATIENT REPORTED OUTCOMES AND PHYSICAL ACTIVITY

RESPONSABLE: Thierry Perez

Background

Dyspnea is a major symptom in respiratory diseases, particularly COPD and asthma. It may also occur in heart failure, obesity, less frequent causes being metabolic, behavioral (hyperventilation syndrome) or neuromuscular disorders. Its prevalence is high in epidemiologic studies, around 25-30 % in middle age or older subjects. It has also a high prognostic significance both in subjects with or without respiratory disorders. The impact of dyspnea on patient reported outcomes, physical limitation and activity is

however ill defined in population studies, particularly in asthma or non-respiratory conditions, most studies being focused on COPD.

Objectives

The main aims of study are to evaluate:

1° the determinants of dyspnea among risk factors, respiratory and non-respiratory diseases, spirometry findings, mood disturbances

2° the burden of dyspnea in patients with respiratory diseases (particularly COPD and asthma) vs subjects without respiratory disorders.

Methods

Dyspnea is assessed in the Constances questionnaire and its main determinants will be sought through a large set of data: anthropometric, risk factors, respiratory symptoms and diseases, spirometry findings, co morbid conditions including cardio-vascular and mood disorders.

The impact of dyspnea will be assessed on health related quality of life (SF12), self-reported activity and physical limitation. During follow up, the correlations between trends in dyspnea intensity and those of other variables will be analyzed, to evaluate more precisely the directionality of these relationships (i.e. the determinants and impact of dyspnea).

Additional evaluations will be performed in a sample of 5000 subjects, including a more precise assessment of dyspnea by the UCSD-SOBQ questionnaire, HAD (anxiety-depression) and IPAQ (physical activity) questionnaires. The PROactive questionnaire will also be added in this sample as soon as available.

Perspectives

Previous studies suggest the major clinical relevance of dyspnea in both the general population and patients with cardio-respiratory disorders. The data obtained in the large Constances cohort including its follow up will provide a better understanding of this symptom. Additional data and analysis may be suggested for the follow up period. These new findings in the general French population should improve the awareness of this major “integrative” symptom, thus allowing better targeted interventions in both public health and individual medical practice.