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## **Developmental determinants in non-communicable chronic diseases and ageing**

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### **Keywords**

asthma; COPD; Paediatric asthma

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Pre-and peri-natal events play a fundamental role in health, the development of diseases and ageing (Developmental Origins of Health and Disease: DOHaD). Research on the determinants of active and healthy ageing (AHA) is a priority: (i) to inform strategies for reducing societal and individual costs of an ageing population and (ii) to develop effective novel prevention strategies.

The European Union (EU) leads a global effort to understand the early determinants of ageing. The Polish Presidency of the EU Council (2011) targeted chronic respiratory diseases in children to promote AHA (1). The developmental determinants of chronic diseases in ageing were reinforced during the Cyprus Presidency of the EU Council (2012). Several projects of the EU Sixth and Seventh Framework Programme for Research and Technological Development (FP6 and FP7) were funded to understand the mechanisms of pre-natal and early life events on the development of chronic diseases. One of the action plans of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) is devoted to integrated care for chronic diseases, and chronic respiratory diseases have been selected as the model for chronic diseases.

As part of this research initiative, a meeting in Montpellier, December 2 and 3, 2013 attempted to better understand the early life events that may impact ageing in health and disease, with a particular focus on respiratory diseases. The results of the FP6 and FP7 projects on population-based cohorts in adults and old age were reviewed to propose novel research, policies and value creation. The full report is in the online supplement and on the MACVIA-LR website ([macvia.cr-languedocroussillon.fr](http://macvia.cr-languedocroussillon.fr)).

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Région Languedoc Roussillon (MACVIA-LR, EIP on AHA Reference Site) University Montpellier 1 CHRU Montpellier and Nîmes MeDALL (Mechanisms of the Development of Allergy, FP7)

European Innovation Partnership on Active and Healthy Ageing: DG Sanco and DG CNECT Framework Programme 7, DG Research and Innovation National Institute of Allergy and Infectious Diseases (NIH)

Proposal following the recommendations of the EU Council of the Polish (2011) and Cyprus (2012) Presidencies Montpellier, 2-3 December 2013

## Importance of life course models to understand healthy ageing and disease

Biological ageing is the progressive deterioration of function that occurs in the post-maturity phase, and can be assessed at the individual, physiological systems and cellular levels (2).

Cross cohort comparisons of British birth cohorts show that social and biological factors from early life onwards can affect ageing, in particular respiratory function and disease.

In order to detect health-promoting factors, the early life events of diseases such as COPD need to be understood (European COST action BM1201: Developmental Origins of Chronic Respiratory Disease (3)). Susceptibility to COPD is associated with markers of foetal growth and early childhood disadvantage. Lung function at birth is determined by *in utero* processes.

Future research needs to develop a life course model of ageing that integrates the rather separate research on specific diseases or clinical conditions, functional ageing and wellbeing and should include socio-economic characteristics.

## Birth cohorts focusing on chronic respiratory diseases in the general population

Asthma and allergic diseases begin early in life. Birth cohort studies are relevant to investigate environmental and lifestyle determinants of asthma and IgE-associated diseases or the absence of such diseases. Over 30 community-based birth cohorts focusing on asthma and allergies have started in Europe and many have been pooled (4). The Network of Excellence GA<sup>2</sup>LEN (FP6, contract N° FOOD-CT-2004-506378) has initiated birth cohort harmonisation. Two Concerted Actions, CHICOS (FP7 No. 241604) and ENRIECO (FP7 grant agreement N° 226285), have built a network of more than 70 birth cohorts across Europe. MeDALL (Mechanisms of the Development of ALLergy, FP7 No. 261357) attempts to generate novel knowledge on the mechanisms of allergy onset and propose early diagnosis, prevention and targets for therapy based on a new standardised follow up of birth cohorts in Europe.

Numerous cohort studies have shown that early decrements in spirometry persist into late middle age, underscoring the crucial importance of early life influences. Optimal lung development depends on normal airway function at birth as well as normal growth during childhood up to the plateau of spirometric function around 25 years of age. After this, lung function declines as a normal event.

The geographical and temporal diversities of birth cohorts in MeDALL provide an excellent opportunity to study the effects of living conditions in different places, since these are likely to be major determinants in the causation of the wave of chronic diseases currently observed.

An NIAID, NHLBI, MeDALL joint workshop (September 2012) (5) has identified over 60 birth cohorts focusing on asthma and allergy worldwide in order to (i) document the knowledge obtained, (ii) identify the knowledge gaps and inconsistencies and (iii) develop strategies for moving forward. Following the workshop in 2012, an online database

containing information about existing cohorts was created to facilitate collaboration ([AsthmaBirthCohorts.nih.gov](http://AsthmaBirthCohorts.nih.gov)).

Some population-based birth cohorts (PIAMA, BAMSE, ECA, MAS) have information on chronic diseases and their risk factors and can assess chronic diseases and AHA across the life cycle.

## Nutrition, obesity and diabetes across the life course

Chronic diseases often start early in life and their processes expand over the life course. DORIAN (Developmental ORigin of healthy and unhealthy AgeiNg: The Role of Maternal Obesity, FP7) aims at linking studies of early developmental processes with those of ageing from a life course perspective.

A better knowledge on the developmental origin of obesity and type-2 diabetes may lead to preventive measures in order to reduce the global epidemic of these two diseases.

Nutrition is vital for health and disease prevention. The Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) Study was a controlled trial (12,741 persons) followed-up for 8 years (1994-2002) to test the efficacy of dietary manipulations in lowering the incidence of chronic diseases and cancer. No supplementation was administered to participants in SU.VI.MAX 2. Food intake and nutritional factors in infancy and childhood have also been studied in several of the ongoing European birth cohorts, which allows for unique longitudinal association analyses on various chronic diseases.

Nutrition is vital to understand the development of chronic diseases and the promotion of healthy ageing.

## Adult cohorts in chronic diseases

The French prospective cohort (E3N), the EPIC-France cohort, is composed of women who were under a health insurance plan, the *Mutuelle Générale de l'Education Nationale*, for schoolteachers and co-workers. In 1990, about 100,000 women (40-65 years) were recruited. Epidemiological research in nutrition, hormones and chronic diseases (asthma, diabetes or osteoporosis) studied the risk factors for developing these diseases.

Two large European epidemiological cohorts, recruited in the early 1990s and followed up for 20 years, have been carried out in respiratory health: (i) the European Community Respiratory Health Survey (ECRHS, <http://www.ecrhs.org/>), including 18,668 individuals aged 20-44 years at baseline; (ii) the Epidemiological study of the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA, <http://egeanet.vjf.inserm.fr>), a French case-control and family study of adults and children at baseline, including 2,120 individuals aged 7-70 years at baseline. Combined analyses between these cohorts have been performed.

COPACETIC, a cohort of the lung cancer screening trial with over 2,200 individuals with lung function and CT scans, identified genes associated with lung function decline in interaction with smoking, CT scan based emphysema and coronary calcifications.

LifeLines (The Netherlands) is a three-generation cohort of 165,000 individuals followed annually by questionnaire and, each 5 years, by extensive functional screening of the 5 prime research areas: (1) metabolic/hormonal, (2) heart/vessel/kidney, (3) lung/respiratory/allergy, (4) psychiatric and (5) musculoskeletal.

Adult cohorts include participants that have been followed up for a long period of time, and may be used to link the development of factor profiles of chronic diseases from early life.

## Old age cohorts

Neuropsychiatric disorders of old-age (eg depression, Alzheimer's disease) may be determined by earlier risk exposure. The DEVELAGE consortium (FP7) aims to characterise shared molecular pathways between the early developmental processes in the brain and brain ageing.

This example underlines the limits of old age cohorts in the study of chronic neuropsychiatric disorder in the elderly.

Integrated research on DEvelopmental determinants of Ageing and Longevity (IDEAL; [www.ideal-ageing.eu](http://www.ideal-ageing.eu), FP7) examines the role of epigenetic regulation and transmission to next generations. A unique human cohort and animal studies are studied to discover novel longevity pathways and the links between development and ageing.

The Three-City Study (3C Study) is a population-based longitudinal study of the relation between vascular diseases and dementia in persons aged 65 years and older. 9,294 participants of both sexes were recruited from three French cities.

CONSTANCES, a large general-purpose epidemiologic population-based cohort, aims to provide public health information. The cohort is a representative sample of 200,000 French adults, aged 18-69 years at inception.

Cohorts in middle and old age adults can be intertwined with earlier cohorts to understand the mechanisms of AHA and diseases in ageing.

Recommendations for future research are reported in the online supplement and the MACVIA-LR website on (i) integration of omics in epidemiologic studies across the life cycle (ii), performance of longitudinal studies assessing chronic diseases and (iii) value of European birth cohorts to study chronic diseases and AHA. Cohorts with an initial focus on chronic respiratory diseases could be expanded to understand the trajectories of chronic diseases and AHA.

Cohorts across the life cycle are essential to understand AHA. Life-long birth cohorts give an overview of the problem and are complemented by cohorts carried out at different ages. Birth cohorts initially focusing on chronic respiratory diseases offer a highly valuable additive information to understand chronic diseases and AHA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>AHA</b>	Active and healthy ageing
<b>BAMSE</b>	Barn Allergi Milj. Stockholm Epidemiologi Projektet
<b>CHICOS</b>	Developing a Child Cohort Research Strategy for Europe
<b>COPACETIC</b>	COPD Pathology: Adressing Critical gaps, Early Treatment & diagnosis and Innovative Concepts
<b>COPD</b>	Chronic obstructive pulmonary disease
<b>COST</b>	European Cooperation in Science and Technology
<b>DARC</b>	Study: Danish Allergy Research Centre study
<b>E3N</b>	Étude Épidémiologique auprès de femmes de la MGEN (Mutuelle Générale de l'Éducation Nationale)
<b>ECA</b>	Environment and Childhood Asthma
<b>EIP on AHA</b>	European Innovation Partnership on Active and Healthy Ageing
<b>ENRIECO</b>	Environmental Health Risks in European Birth Cohorts
<b>EPIC</b>	European Prospective Investigation into Cancer and Nutrition
<b>EU</b>	European Union
<b>FP</b>	Framework Program for Research and Technological Development
<b>GA<sup>2</sup>LEN</b>	Global Allergy and Asthma European Network
<b>MACVIA-LR</b>	Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc Roussillon (EIP on AHA Reference site)
<b>MAS</b>	Multi-centre Allergy Study
<b>MeDALL</b>	Mechanisms of the Development of ALLergy
<b>NHLBI</b>	National Heart Lung and Blood Institute
<b>NIAID</b>	National Institute of Allergy and Infectious Diseases

**NIH**

National Institutes of Health

**PIAMA-NHS**

The Prevention and Incidence of Asthma and Mite Allergy -Natural History Study



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