AUDIT, RESEARCH AND GUIDELINE UPDATE

Developmental determinants in non-communicable chronic diseases and ageing

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ABSTRACT
Prenatal and peri-natal events play a fundamental role in health, development of diseases and ageing (Developmental Origins of Health and Disease (DOHaD)). Research on the determinants of active and healthy ageing is a priority to: (i) inform strategies for reducing societal and individual costs of an ageing population and (ii) develop effective novel prevention strategies. It is important to compare the trajectories of respiratory diseases with those of other chronic diseases.

Prenatal and peri-natal events play a fundamental role in health, 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 to: (i) inform strategies for reducing societal and individual costs of an ageing population and (ii) 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 prenatal and early life events on the development of chronic diseases. One of the action plans of the European Innovation Partnership 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 on 2 and 3 December 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).

IMPORTANCE OF LIFE COURSE MODELS TO UNDERSTAND HEALTHY AGEING AND DISEASE
Biological ageing is the progressive deterioration of function that occurs in the postmaturity 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 well-being 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^{2}LEN (FP6, contract No FOOD-CT-2004-506378) has initiated birth cohort harmonisation. Two concerted actions, CHICOS (FP7 No. 241604) and ENRIECO (FP7 grant agreement No 226285), have built a network of more than 70 birth cohorts across Europe. Mechanisms of the Development of ALLergy (MeDALL, FP7 No. 261357) attempts to generate novel knowledge on the mechanisms of allergy onset and proposes 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 and MeDALL joint workshop (September 2012)[5] 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.niaid.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 ORigins 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 coworkers. 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 and (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 2120 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 2200 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, every 5 years, by extensive functional screening of the five 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; 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. A total of 9294 participants of both sexes were recruited from three French cities.

CONSTANCES, a large general-purpose epidemiological 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 epidemiological 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. Lifelong 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 highly valuable additive information to understand chronic diseases and AHA.

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Correction notice This article has been corrected since it was published Online First. The statement 'PG and JPA did not participate in the discussion' on the title page has been removed. It has now been corrected and included in the 'Contributors' statement.

Contributors All authors participated in the meeting. All authors contributed to the discussion, except for KB and JPA.

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THORAXJNL-2014-206304

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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

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Abbreviations

AHA: Active and healthy ageing
AMICS: Asthma Multicentre Infant Cohort Study
BAMSE : Barn Allergi Milj. Stockholm Epidemiologi Projektet
CHICOS: Developing a Child Cohort Research Strategy for Europe
COPACETIC: COPD Pathology: Adressing Critical gaps, Early Treatment & diagnosis and Innovative Concepts
COPD: Chronic obstructive pulmonary disease
COST: European Cooperation in Science and Technology
DARC:Study: Danish Allergy Research Centre study
DOHaD: Developmental Origins of Health and Disease
E3N: Étude Épidémiologique auprès de femmes de la MGEN (Mutuelle Générale de l'Éducation Nationale)
ECA: Environment and Childhood Asthma
EIP on AHA: European Innovation Partnership on Active and Healthy Ageing
ENRIECO: Environmental Health Risks in European Birth Cohorts
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EPIC: European Prospective Investigation into Cancer and Nutrition
EU: European Union
FP: Framework Program for Research and Technological Development
GA^{2}LEN: Global Allergy and Asthma European Network
GINI-B: German Infant Nutritional Intervention-Study
KOALA: Kind, Ouder en gezondheid, Aandacht voor Leefstijl en Aanleg
LISA: Influences of Lifestyle-related Factors on the Immune-system and the development of allergies
MACVIA-LR: Contre les MAladies Chroniques pour un VIeillissement Actif en Languedoc Roussillon (EIP on AHA Reference site)
MAS: Multi-centre Allergy Study
MeDALL:Mechanisms of the Development of ALLergy
NHLBI: National Heart Lung and Blood Institute
NIAID: National Institute of Allergy and Infectious Diseases
NIH: National Institutes of Health
PARIS: Pollution and Asthma Risk: an Infant Study
PIAMA-NHS: The Prevention and Incidence of Asthma and Mite Allergy -Natural History Study

Introduction

Poor health is largely shaped by chronic diseases which share common risk and socio-economic factors, biological mechanisms and cluster in co-morbidities. These are intertwined with ageing and represent a major cause of frailty [1]. Pre-and peri-natal events play a fundamental role in health, the development of chronic diseases and ageing (Developmental Origins of Health and Disease: DOHaD) [2]. Links between environmental and behavioural factors with epigenetic mechanisms [3-5] and conserved genes [6, 7] have been proposed. Ageing is regulated by several pathways including telomer dysfunction related to the senescence of tissues and cells [8]. Like other organ systems, the immune and metabolic systems are highly vulnerable to environmental changes, and is also highly influenced by internal molecules such as hormones [9] and ageing [10]. Research on the determinants of healthy ageing has become a priority to inform strategies for reducing societal and individual costs of an ageing population and to develop effective novel prevention strategies to promote active and healthy ageing (AHA) [11].

1- European Union activities

The European Union (EU) is at the fore front of the global effort to better understand early determinants of ageing.

The 2010 Council of the European Union prioritised the understanding, prevention and management of chronic diseases [12]. The Polish Presidency of the EU Council (2011) targeted chronic respiratory diseases in children to promote their early recognition, prevention and management to ultimately impact AHA [13]. The developmental determinants of chronic diseases in ageing have been reinforced during the Cyprus Presidency of the EU Council "Healthy ageing across the lifecycle" (2012) [14].

Several projects of the EU Seventh Framework Programme for Research and Technological Development (FP7) have attempted to understand the mechanisms of pre-natal and early life events on the development of chronic diseases and ageing. Epidemiologic studies across the life cycle combined with appropriate omics data may help to define pathways and biomarkers of healthy ageing. Research and innovation are key contributors for achieving the goals of the Europe 2020 strategy: growth, jobs, competitiveness, quality of life and social inclusion. The new EU framework for research, called Horizon 2020, will be one of the main tools to implement the Innovation Union policy. The joint strategic EC-COST workshop "Relationship between genome and epigenome", held 14-15 February 2013 in Brussels, addressed the links between genetic, epigenetic and non-genetic factors throughout the lifespan and across generations, their role in disease susceptibility and disease progression and the associated challenges of data handling/storage and interpretation. The outcomes of the workshop set the vision for future policies and research agendas at European level

European Innovation Partnerships (EIP) aim to enhance EU competitiveness and tackle societal challenges [15]. Active and Healthy Ageing (AHA) is a major societal challenge, common to all European countries and all populations. The EIP on AHA has 6 action plans, one of them devoted to integrated care for chronic diseases.

2- Objectives of the meeting

The Région Languedoc Roussillon is deeply involved in chronic diseases and AHA through MACVIA-LR (Reference site of the EIP on AHA) [16, 17], and the Président, Mr C Bourquin, has given an unrestricted grant to support this meeting.

Following the EU efforts over the last 10 years in cohort investigations across the life cycle, a meeting was convened in Montpellier, December 2 and 3, 2013 in order to better understand early life events that may impact ageing in health and disease. The results of the FP6 and FP7 project on pre-natal and early life events in chronic diseases were confronted to population-based cohorts in adults and old age to propose novel research, policies and value creation. The programme and abstracts of the meeting are presented in the online supplement.

3- Reducing health inequalities in France as an example of priorities in the EU

Non-communicable diseases represent a WHO, UN and EU priority [18]. Life course epidemiology research is a key priority of the French Institute of Public Health (ISP), the institute covering the public health disciplines (biostatistics, epidemiology and social sciences applied to health) of the Health and Life Sciences Research Alliance (AVIESAN). These priorities are in line with the WHO Commission on Social Determinants of Health [19]. The "French paradox" gives a particular importance to the recommendations of this report for a better understanding of health inequalities and for promoting and evaluating public policies aimed at reducing them. While France ranks high on some health indicators (2nd longest life expectancy for females, 7th for males, high quality of its health system, etc...), it is also the one country in Western Europe with mortality and morbidity inequalities [20, 21]. A better understanding of the complex causal chains which translate social differences in health inequalities and higher exposure to morbidity and premature mortality, and how they affect populations at various ages, is therefore a key priority for French public health research [11]. Promoting life-cycle epidemiology and its interdisciplinary dialogue with both social sciences and biomedical sciences is clearly a major need for reaching this goal.

4- 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 [22, 23]. In depth studies and cross cohort comparisons of British birth cohort and life course studies are providing growing evidence that social and biological factors from early life onwards can affect the peak function achieved at maturity and the rate of functional decline at all these levels; and this has consequences for wellbeing, quality and length of life [24, 25].

In order to detect health-promoting factors, it would be helpful to understand the inverse, ie factors that promote disease. Multiple independent approaches are currently researching the developmental origins of NCDs. Understanding the early life determinants of diseases such as COPD is relevant and the focus of the European COST action BM1201: Developmental Origins of Chronic Respiratory Disease [26]. COPD is a significant cause of morbidity and mortality. Susceptibility to COPD is associated with markers of foetal growth and markers of early childhood disadvantage. Lung function at birth is determined by *in utero* processes (e.g. low birth weight babies or mothers who smoked during pregnancy). Many genes that are associated with spirometry in adult life are also associated with lung function in childhood and infancy [27].

> 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 include socio-economic characteristics.

5- Birth cohorts in the general population

Asthma and allergic diseases, the most common disorders in children, begin early in life, but no effective preventive interventions exist to date. Birth cohort studies are a relevant research strategy to investigate the environmental and lifestyle determinants of asthma and atopic disease as well as the absence of such diseases. They could therefore act in health promoting identification. The prioritised research agenda of WHO for the prevention and control of chronic respiratory diseases also includes follow up of cohorts in developing countries to better understand disease onset, progression or disappearance [28].

More than 30 community-based birth cohorts focusing on asthma and allergies have started in Europe over the past 25 years. By 2014/2015, the first two European birth cohorts on allergy and respiratory diseases from the UK (Isle of Wight 1989) [29-31] and Germany (MAS 1990) [32-38] are reaching 25 years of age, followed by others that are soon approaching 18-20 years, such as BAMSE (Sweden) [39-41], ECA (Norway) [42-46], PIAMA (NL) [47-50], GiniPLUS, LISA (both Germany) [51, 52], AMICS-Menorca (Spain) [53, 54] and DARC (Denmark) [55]. Among the younger European birth cohorts are KOALA (NL) [56, 57], INMA (Spain) [58, 59], PARIS (France) [60, 61], EDEN [62] and others with special interest in environmental risk factors for chronic diseases.

In Europe, the Network of Excellence GA^{2}LEN (FP6, contract N° FOOD-CT-2004-506378) [63-65] has initiated the harmonisation of birth cohorts [66]. ENRIECO (FP7 grant agreement N° 226285) [67, 68], another initiative built on the GA^{2}LEN experience [69], assessed the effects of outdoor and indoor air pollution, and compared pooled analysis with de-centralised coordinated meta-analysis. The two Concerted Actions, CHICOS (FP7 grant agreement No. 241604) and ENRIECO, have built a network of more than 70 birth cohorts across Europe that are prospectively studying more than 500,000 mothers, fathers and children.

Following the experience of these projects, MeDALL (Mechanisms of the Development of ALLergy, FP7 grant agreement No. 261357) [70, 71] was conceived to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention and targets for therapy

based on existing information and a new standardised follow up of birth cohorts in Europe. Using the DataSHaPER methodology [72, 73], historical pooled data were harmonised from 14 birth cohorts, representing over 40,000 participants, covering 130 variables and 125 individual data generation events (follow-ups) requiring almost 3,000 mapping decisions [74].

The MeDALL study found that comorbidities are of major importance for chronic respiratory and allergic diseases in childhood, and that IgE sensitisation is adding its effects on top of them [75]. Such a finding could not have been observed when individual cohorts were analysed due to an insufficient number of subjects. A standardised follow-up questionnaire, interoperable with the historical one, made it possible to follow over 11,000 children, many of them up to the age of 18 years [76]. The harmonisation and knowledge management strategies developed by MeDALL, combining retrospective and prospective data, offer a high statistical power to assess trajectories of lifestyle and environmental exposures and to study multidimensional trajectories of chronic respiratory and allergic symptoms using "unsupervised" statistical techniques. They can now be applied to provide efficient opportunities for collaborative studies across the life cycle. An open data approach can extend the benefits of such collaborations to the full society.

Numerous cohort studies have shown that early decrements in spirometry persist into late middle age, underscoring the crucial importance of early life influences [77, 78]. Optimal lung development depends on normal airway function and birth at birth, and 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) has provided the opportunity to consider more ambitious initiatives identifying over 60 birth cohorts focusing on asthma and allergy worldwide which have been initiated in the last 30 years in order to (1) document the knowledge that asthma/allergy birth cohorts have provided, (2) identify the knowledge gaps and inconsistencies and (3) develop strategies for moving forward, including potential new study designs and the harmonisation of existing asthma birth cohort data. This database will be updated as more cohorts are identified.

> Following the workshop in 2012, an online database containing information about existing cohorts was created to facilitate collaboration (AsthmaBirthCohorts.niaid.nih.gov).

The Project Viva is a U.S. pre-birth cohort study of prenatal and early-life determinants of growth, adiposity, cardiovascular risk factors, cognition, and respiratory disease and intermediate metabolic, inflammatory and epigenetic marks that may be on pathways that influence these outcomes [79-81]. While Project Viva investigators have focused on prenatal maternal diet and dietary supplements as primary exposures, they have ascertained many additional co-exposures and potentially modifying factors both in early-life and in later childhood [82].

In the PIAMA birth cohort study, there is yearly information on height and weight as well as on lifestyle and environmental factors [83]. Starting at age 8, chronic disease parameters were included (eg cholesterol, HbA1c, random glucose, blood pressure, lung function and hyperresponsiveness), and at age 16, also intima media thickness [84]. Similar clinical and epidemiological data are available in other European birth cohorts (e.g. BAMSE, ECA and MAS). These additional measurements make it

possible to study the levels and development of cardio-metabolic endpoints from age 8 onwards through puberty and the associations with early life risk factors.

Some population-based birth cohorts have information on chronic diseases and their risk factors. They can be of great interest to assess chronic diseases and healthy ageing across the life cycle.

6- Nutrition, obesity and diabetes across the life course

The global epidemic of obesity was soon followed by an epidemic of type 2 diabetes in adults and it is starting to appear in earlier ages more recently. These chronic diseases have genetic and developmental origins and physiopathological processes expanding over the life course. Although diabetes is usually diagnosed after 50 years of age, obesity has developed across the life cycle. Foetal and early life events are of great importance [85, 86]. As examples, in France, thinness rather than obesity in childhood and adolescence is the most common pathway to type 2 diabetes in middle age and older adults [87]. Obesity in pregnancy promotes accelerated foetal growth and gestational diabetes that increase the offspring susceptibility to childhood obesity and type 2 diabetes at an earlier age.

DORIAN (Developmental ORigins of healthy and unhealthy AgeiNg: The Role of Maternal Obesity, FP7 NO 278603) aims at linking studies of early developmental processes with those of ageing from a life course perspective. As a consequence of maternal obesity, the offspring will present early disease features, predisposing to the development of cardiovascular disease, type 2 diabetes and cognitive impairment. The project focuses on the involvement of insulin resistance and glucocorticoid overexposure, oxidative stress or inflammation, telomere shortening, and epigenetic changes.

A better knowledge in 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. The Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) Study was a randomised double-blind, placebo-controlled trial including 12,741 persons followed-up for 8 years (1994–2002) to test the efficacy of dietary manipulations in lowering the incidence of cancer, ischemic heart disease, and overall mortality [88, 89]. At the end of the trial phase, participants were invited to participate in an extended follow-up on a voluntary basis. 6,850 subjects were included in the observational SU.VI.MAX 2 Study (2007–2009) for a new clinical examination focusing on cognitive and functional capacities. In addition, participants completed a self-administered questionnaire providing information about health and life-style [90]. 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.

7- Adult cohorts in chronic diseases

The French prospective cohort (E3N) [91], the EPIC-France cohort [92, 93], is composed of women who were under a health insurance plan, MGEN (*Mutuelle Générale de l'Education Nationale*), for schoolteachers and co-workers. In 1990, about 100,000 women aged 40-65 years were recruited. Blood samples were collected from approximately 25% of the participants, and saliva samples from almost 50%. About 75,000 of the E3N women answered the diet history questionnaire sent in 1993. Analytical epidemiological research in nutrition, hormones and chronic diseases (e.g. asthma [16],

diabetes [94] or osteoporosis [95]) has been carried out to understand the risk factors for developing cancer and other major diseases.

Two large European epidemiological cohorts, recruited in the early 1990s and followed up for 20 years, have been carried out in respiratory health. The European Community Respiratory Health Survey (ECRHS, http://www.ecrhs.org/, FP3) is an international population-based study of asthma and allergy, including 18,668 individuals aged 20-44 yr at baseline [96, 97]. The Epidemiological study of the Genetics and Environment of Asthma, bronchial hyperresponsivness and atopy (EGEA, http://egeanet.vjf.inserm.fr) is a French case–control and family study of adults and children at baseline, including 2,120 individuals aged 7-70 yr at baseline [98, 99]. Combined analyses between these cohorts have been made [100]. The studies can appraise the trajectories of participants concerning respiratory diseases (onset, persistence, disappearance).

COPACETIC (FP7 N° 201379) is a cohort of the lung cancer screening trial with over 2,200 individuals with lung function and CT scans. The study identified genes associated with lung function decline in interaction with smoking, CT scan based emphysema and coronary calcifications [101].

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 [102].

> Adults cohorts have followed up participants for a long period of time and may be used to link development of factor profiles of chronic diseases from early life.

8- Old age cohorts

Neuropsychiatric disorders of old-age may be determined by earlier risk exposure. Late-life depression is modulated by exposure to childhood adversity interacting with genetic vulnerability, and the principal risk factors for Alzheimer's disease appear to occur principally in early adulthood [103, 104]. Current knowledge is insufficient to identify the transition of normal brain ageing into Alzheimer-like brain damage. The aim of the DEVELAGE consortium is to characterise shared molecular pathways between 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, FP7) examines the role of epigenetic regulation and transmission to next generations. A unique human cohort and animal studies (including fruitflies and Xenopus) are being studied in order to discover novel longevity pathways and to determine whether they affect the link between development and ageing [105, 106]. To find set-points of epigenetic control, genome-scale analyses and studies of specific gene systems such as histone methylation of homeobox genes at different embryonic stages are compared. Epigenetic responses are linked with phenotypic consequences of early developmental conditions with biomarkers of the ageing rate.

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 [107, 108 , 109]. A total of 9,294 participants of both sexes were recruited from three French cities: Bordeaux (South-West), Dijon (North-East) and Montpellier (South-East). The 3C Study started in 1999 and produced information on life habits, nutrition, hypertension, depression, genetics, other risk factors of dementia and neuroimaging.

CONSTANCES is a large general-purpose epidemiologic population-based cohort in epidemiologic research to provide public health information. The cohort is a representative sample of 200,000 French adults aged 18-69 years at inception. Data are prospectively collected from different sources: annual self-administered questionnaire, periodic health examinations, linkage to health and social national administrative databases. Subjects over 45 years will have a comprehensive work-up of functional physical and cognitive capacities. The data include social and demographic characteristics, social status, life events, behaviours, and occupational factors.

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

9- From science to policies and value creation

K Berkouk

The European Innovation Partnership for Active and healthy Ageing reflects a growing awareness that better care in an ageing society calls for innovative ways to address the needs of older people and improved understanding of the mechanisms of ageing.

10- Recommendations

Recommendations for future research were developed in 3 breakout sessions.

Breakout Session 1: How to integrate omics in epidemiologic studies across the life cycle

Population-based studies enriched by patient populations are of interest to be used for sampling of omics. Tissues and cells (Peripheral blood cells, T and B cells, airway epithelial cells can be studied in many biological fluids and biopsies [110], but most cohorts only have blood and/or urine samples as they are easy to collect, process, and store, and also carry the strongest implications for intervention at the population level. Recently, several cohorts (VIVA, PIAMA) have implemented collection of nasal epithelial cells to be able to address the role of airway epithelial mechanisms.

To integrate omics across the life cycle, multiple cohorts with information on risk factors and diseases should be investigated at different stages of the life (infants, children, adults, old age). The time of study and trajectories embedding acute and chronic effects of risk factors and disease co-morbidities need to be characterised. As biomarkers can change over time, susceptibility to reverse causality and residual confounding is a potential limitation of these studies.

Omic studies need to be based on research questions. The sample size and availability of biological samples should be carefully determined *a priori*.

Candidate biomarkers and pathways have raised remarkable interest in clinical and epidemiological research [111]. They can improve the understanding molecular mechanisms of diseases, predict models of complex diseases, refine disease phenotypes and guide treatment responses [112, 113]. Much of the research to identify new biomarkers has evolved from studies has focused on genetics and genomics.

- For genomics, whole genome DNA sequencing is now favoured, but many cohorts have historical data from genome-wide association studies (GWAs) [114], which may be used.
- Several types of epigenomic studies can be performed to complement and expand genomic data, including DNA methylation, short and long noncoding RNAs [115], chromatin marks [116] or chromatin contact maps [7, 117].
- Transcriptomic profiling using RNA sequencing or up-to-date microarray platforms can give valuable insights about gene expression patterns related disease and exposure. Studies on

epigenetics and transcriptomics, may need to be investigated in a specific cell type, given the tissue specificity [118].

- Proteomic analysis is still limited by the sensitivity of the current technology and its ability to expand the information provided by epigenomic analysis may need to be investigated in a specific cell type before adopting it in large-scale applications. Using current proteomics technology, protein wide analysis of cells and tissues is not yet feasible with, coverage of all protein isoforms and post-translational modifications within the large dynamic concentration range of proteins. Therefore, targeted proteins need to be selected for further study. Future initiatives, such as the Human Proteome Project, may change this concept [119].

- Integration of genetic, epigenetic, transcriptomic and proteomic data (integrative genomics) may assist in determining causal networks that lead to disease development [120].

- For all these studies, bioinformatic applications are of vital importance and must be carefully planned right from the beginning of the project strategy.

Breakout Session 2: Longitudinal studies assessing chronic diseases Breakout Session 2: Longitudinal studies assessing chronic diseases and ageing

D Postma (NL)

It is now widely recognised that ageing is largely determined during the life course, including the pre-birth period. One of the main outcomes of the discussion was that aging can be defined as a collapse of compensatory mechanisms. This session contributed to shed some light on several crucial questions by turning traditional projects into innovative ones.

As a basics the following reasons for studying healthy ageing were mentioned: (1) political agenda (consumer costs reduction); (2) biological pathway identification for early intervention and late preventive strategies ; (3) personal well being.

The research questions to do so need to be well defined including (1) biological ageing, (2) frailty, (3) aggregated measures of ageing in elderly cohorts and (4) active and healthy ageing.

Several types of cohorts should be studied: including population-based, disease-oriented, case-control studies and GP databases. In these studies, environmental changes and concurrent findings should be confronted with genomics. In long-term studies, the methodology to assess questions, diagnosis and coding of disease may have changed and should be considered. Retrospective and prospective studies do often not provide similar results: so also birth cohorts with prospective longitudinal design are necessary.

Some specific questions need to be answered:
- Can we disentangle the respective contribution of normal advance in age and chronic diseases to the health consequences of ageing?
- What are the most satisfying models of the life course (critical periods, accumulation, pathways)?
- Should we consider different models according to specific chronic diseases (COPD, neurodegenerative diseases, musculoskeletal disorders…)?
- Can we develop beter methods for cross-cohort and cross-data-type integrative analysis?

Breakout Session 3: Impact of European birth cohorts on chronic diseases and healthy ageing

MeDALL has created a new cross-European birth cohort including now over 35,000 children and their families with clinical data on lung function, body mass index, skin prick tests, house dust samples prospectively collected since early childhood, blood pressure and biomaterial including cord blood, breast milk, serum/plasma, saliva, urine, and stool samples. The prospective regularly collected subjective data include pregnancy (smoking, stress, etc), allergic and respiratory symptoms, doctor

diagnoses, respiratory infections, vaccinations, physical activity, dietary habits, socio-economic characteristics, family lifestyle, home environment, parental and siblings' medical history, etc.

This **unique health data source** will help to address relevant research questions examining:

- The development of respiratory and allergic diseases from childhood to adulthood and old age (sensitisation, disease, lung function decline, COPD).
- The effect of allergy/asthma in young age on lung function decline and COPD in older adults.
- Childhood determinants (e.g. perinatal factors, obesity, dietary habits, physical inactivity, lower social status, stress and environmental exposures) for lung function decline in early adulthood (later leading to chronic resp. diseases)
- The observed links between allergy/asthma and cancer, autoimmune disorders, other inflammatory diseases, infections, heart disease, mental illnesses, etc.
- The links between early life events and chronic diseases using a common questionnaire for chronic diseases, in particular in the 20-25 year old participants of the cohorts.
- The links between early life events, chronic diseases in adulthood and healthy ageing using the harmonisation method of MeDALL.
- The application of large-scale genetic, epigenetic, transcriptomic and proteomic profiling related to onset and progress of chronic diseases.
- Factors associated with lack of disease.

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