What is chronic obstructive pulmonary disease (COPD) and why is it becoming more prevalent in both high and low income countries?

COPD is a disease where inflammation in the airways causes increasing breathing difficulties. We do not fully know why COPD is becoming more prevalent. Increased smoking among women post-World War II is certainly of importance; whether this will also play a role for their offspring remains to be seen. Indoor open fires and survival beyond young age may contribute in low income countries, and one may speculate whether a COPD epidemic will follow the asthma one.

How much evidence is there to suggest that an individual’s antenatal environment influences chronic respiratory disease?

There is quite a lot of evidence that antenatal environment is important for asthma in children, and multiple children’s cohorts are steadily increasing our knowledge in this field. There is naturally much less evidence of early-life influences on adult chronic respiratory disease, and there is very scarce evidence when it comes to early-life influence on lung ageing in adulthood. Our study of index cohorts provides some evidence of early-life influence on adult respiratory health, and one may speculate whether a COPD epidemic will follow the asthma one.

Can you describe the overall aims of your investigation? What are you setting out to achieve?

We want to study the causes of asthma, allergy and COPD during the life course, including heritable effects of environmental influences. Through this, we seek to harness an understanding of which environmental factors are of importance during which age windows.

How does this research adopt a new approach compared with other projects that seek to determine the underlying causes of COPD?

Through our approach, the aim is to investigate COPD from a lifespan and transgenerational perspective. Usually, COPD is studied in elderly subjects, where relating this disease of old age to early-life environment is almost impossible. In contrast, our study employs data from three generations, and will be able to assess early-life risks associated with lung function decline and COPD in both young-elderly and elderly subjects, while disentangling heritable components. This will give a new understanding of COPD development and its early-life origins, which will, in turn, yield information about COPD emerging in younger generations. Almost all existing knowledge of COPD relates to COPD of past generations; it is not unlikely that COPD will be different in emerging generations and low income societies.

Could the airway and gut microbiome impact the onset and progression of immunological diseases? From where has this hypothesis arisen?

The airway and gut microbiome are highly relevant for immunological disease. We contributed to the development of the so-called hygiene hypothesis a decade ago, showing that those who kept dogs in childhood had less allergy in adulthood. This was consistent over geographical and cultural borders, and we have suggested that dogs could provide beneficial microbial immunological stimulation. Recently, it was demonstrated that microbial diversity accounts for the finding of less allergy in children who live on farms, and studies using genetics methodology applied to the microbiome have revealed that the gut microbiome plays a central role for systemic inflammation. Our study will bring this area forward by relating extensive exposure characterisation of the index subjects with health and disease of the offspring.

In what ways do you anticipate the study will enhance understanding of the causal factors and preventable risks of asthma, allergy and COPD?

Most studies investigate one age group, eg. children, adults or the elderly. This study will be able to address these diseases from a lifespan perspective and provide good information on environment, including before conception. From a public health perspective, this study will enable us to fully understand the magnitude of specific preventable risks, including transgenerational environmental risks, and the ages at which they operate. Meanwhile, from a scientific point of view, the study will bring a new understanding of the life course development of asthma, allergy and COPD and thus generate important hypotheses on causal pathways that may be further investigated in animal models.
UNCOVERING WHAT’S FUNDAMENTAL – AND WHEN

In order to fully study the causes of asthma, allergy and COPD during the life course, the project is discerning which environmental factors are of importance during certain age windows. Here, a key component is to determine the full effects of smoking tobacco, including: transgenerational epigenetic changes from parental and grandparental smoking before conception; intrauterine exposure; childhood passive smoking; and active smoking during adolescence and adulthood.

Understanding these factors would allow the team to design the most efficient and effective prevention strategies, and would give experts a more rounded insight into lung disease development and its relation to the environment.

UNDERSTANDING AIRWAYS DISEASES

Knowledge of COPD remains quite rudimentary: it progresses gradually over a number of years, with early symptoms as innocuous as wheezing or laboured breathing after exercise. In its advanced stages, however, sufferers may be confined to a wheelchair, with even the slightest activity causing breathing problems. The study has sought to establish relationships with numerous research environments in lower middle income countries (LMICs), with the aim of integrating study centres from these areas. Indeed, the key challenge of the project is ensuring a high response rate from all research centres: though northern Europe has the luxury of extensive registry data, other centres, in other locations, will have to research much deeper to identify offspring. Many subjects will have already given much of their time to help the study, and so may be reluctant to assist further; others may have moved away, which would require the utilisation of a so-called study bus, as opposed to traditional, stationary laboratories.

Another challenge concerns the ability to benefit properly from the valuable yet complex sets of data amassed through the research. To reap the full advantages of the project, without getting lost in the realm of possibility, highly focused and intelligent research is required, along with synergistic collaboration between centres and researchers.

As for the present stage of the project, the third follow-up of index subjects from the centres is almost complete: “Information about offspring has been obtained from some 12,200 parents, and we have started working with first analyses in order to begin developing methodology for generation data,” Svanes reveals. “One study centre has already clinically investigated 350 adolescent offspring.” Experiences from this will serve for first analyses and for fine-tuning the clinical

OBSTRUCTIVE AIRWAYS DISEASES are increasing at an unprecedented rate. No longer synonymous with elderly male smokers, the diseases are now affecting nations on an indiscriminate level, with chronic obstructive pulmonary disease (COPD) speculated to become the world’s third largest killer by 2030. The reason for the increase in these diseases remains unclear, with little research being carried out in lower income countries, and only speculation regarding causes other than smoking.

The RHINESSA project, which is being led by the University of Bergen, is seeking to understand the transgenerational and life-course perspective on environmental and lifestyle factors in relation to asthma, allergy and COPD. Led by clinical pulmonologist, Dr Cecilie Svanes, the study is investigating the role of preventable environmental and lifestyle factors, before conception and throughout an individual’s lifetime, for obstructive and allergic airways diseases. It is analysing tobacco smoke and other air pollutants to understand respiratory health in offspring. Allergens and microbial factors are also being studied, along with metabolic and hormonal factors such as weight, diet, nutrition and physical activity. RHINESSA assesses the timeframes within development when these risks are more apparent, as well as the heritability in disease characteristics. The project further compares main risk associations between generations, and predicts the preventability of such stiffling diseases.

RHINESSA is integrated with previous, highly successful studies in the field, as Svanes explains: “The study will investigate offspring and parents of three well-known respiratory health population studies: ECRHS, RHINE and SAPALDIA, which followed adults over 20 years with detailed characterisation of health and environment”. These investigations have already led to important advancements in knowledge, disseminated in over 500 scientific papers. Rather than starting all over again with a new cohort, RHINESSA will study the offspring and parents of these people. Indeed, this method gives the researchers free data concerning the early-life environment of offspring, with additional information about grandparents and insight into the environment before conception.

Preventative strategies to stop chronic obstructive pulmonary diseases – one of the world’s biggest killers

And breathe…

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INTRODUCTION

RHINESSA

TRANSGENERATIONAL AND LIFE-COURSE PERSPECTIVE ON ENVIRONMENTAL AND LIFE-STYLE FACTORS IN RELATION TO ASTHMA, ALLERGY AND COPD

OBJECTIVES

To study environmental and lifestyle factors in relation to asthma, allergy and chronic obstructive pulmonary diseases (COPD) from a transgenerational and life-course perspective, by investigating the influence of smoking, obesity and the microbiome for these diseases over the lifespan of three generations, to assess the relative importance of exposure before conception and at different stages of life.

PARTNERS

Bergen Respiratory Research Group, University of Bergen: Cecilie Svanes; Ane Johannessen; Francisco Gomez Real; Trude D Skorge and Ernst Omenaas; Aarhus University: Vivi Schlünssen (assistant project coordinator) and Torben Sigsgaard; SAS & University of Huelva: José Antonio Maldonado; Antonio Pereira and José Luis Sanchez; Albacete University Hospital: Jesus Martinez-Moratalla; University of Melbourne: Shyamali Dharmage and Michael Abramson; University of Iceland: Thorarinn Gislason and Bryndis Benediktsdottir; Swiss Tropical and Public Health Institute: Julia Dratva and Elisabeth Zemp; University of Tartu: Rain Jogi; University of Uppsala: Christer Janson; Eva Lindberg and Dan Norbäck; University of Umea: Lennart Bråbäck and Bertil Forsberg; University of Gothenburg: Kjell Toren

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WHERE NEXT?

In terms of the future, Svanes is clear: “Moving forward, the perspective will be to use information from the three-generation study in planning intervention in the fourth generation and in selected LMICs, in co-work with expertise in metal and childhood development, as well as international health and intervention methodology”. The project will yield new insights into epigenetic mechanisms and transgenerational environmental effects; the developmental origins of chronic disease; and the role of microbiota and microbial environment in immunologic and inflammatory development. Taken together, this marks an era of exciting research opportunities in asthma, allergy and COPD.

This marks an era of exciting research opportunities in asthma, allergy and COPD

protocol of adolescent offspring, while teams of trained field workers will start investigating the offspring generation from this March.

RHINESSA also aims to determine the effects that grandparents’ microbial environments have on the asthma and allergy in young people today. Thus, it is assessing generational microbial environments, as well as microbiome and disease, during the life course. Lastly, the team is looking into the effects of obesity and weight on chronic lung disease, and how the maternal metabolic system affects the susceptibility of metabolic disease in children. The goal is to see whether it is possible to prognosticate respiratory health effects of the global obesity epidemic and identify the age windows where prevention strategy is best implemented.

The results will also help influence policy makers, acting as a foundation for health education. Insight into the importance of risks and age windows will allow policy makers to designate resources to preventative and intervention strategies. This, it is hoped, could have a global impact, with particular resonance for LMICs, in which obesity and air pollution is increasing, the microbial sphere is constantly changing, and the possibility for intervention is hindered by economic hardship. The study could also shape clinical guidelines, recognising the age windows most susceptible to risk, and forming the basis for preventative strategy. It will furthermore lay the groundwork for the education of patients and families in terms of preventative strategies. Another line of ensuing research will be epigenetic, focusing on molecular pathways that are not eliminated at conception. Epidemiologic research and data will be reproduced for different societies and nations, with the knowledge of age windows used to further research the molecular functions of environmental and lifestyle factors. The study continues, but is more pressing than ever.