

PROPOSAL FOR A NESTED PROJECT (1.10.2008)

(within the frame of SNF grant 33CSCO-108796)

Preparation of THE SAPALDIA OFF-SPRING STUDY

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Project team (by alphabetical order): Prof. Nino Kuenzli (scientific advisor), Dr Denise Felber (coordinator SAPALDIA 3), Prof Sally Liu (exposure assessment), PD Dr Elisabeth Zemp (gender research and scientific advisor)

I. Project outlines:

1. Background and rationale:

Most recent findings from experimental and human studies make it clear that the enhancement of knowledge about the causes of complex chronic diseases will require an expanded integrated approach taking into account not only endogenous and exogenous determinants of health but also the time windows of exposure and interactions between exogenous exposures, the expression of genes and other endogenous causes of health and disease.

Early life time and in particular life in utero are considered periods of amplified susceptibility to adverse effects of exogenous and endogenous causes of diseases. Many chronic diseases, such as cardiovascular and respiratory diseases, occurring in later life may in part be explained by priming factors experienced in early life¹⁻¹⁰.

Recent studies indicate early life exposure to ambient air pollution – the most prevalent and ubiquitous environmental hazard in most parts of the world – to be associated with adverse birth outcomes¹¹⁻¹⁸, as well as with reduced lung growth^{10 19-21} and the development of asthma and allergies during childhood²²⁻²⁹. Epidemiological and experimental studies have confirmed air pollution to induce systemic inflammation response³⁰⁻³⁵. A large body of evidence supports the theory of acute and long term effects of air pollution on the development of cardiovascular disease in adults³⁶⁻⁴³. There is, however, a gap in the knowledge of the systemic and cardiovascular response to air pollution in childhood. Similarly, the role of diet and nutrition during pregnancy and in the first years of life may have important implications on the future development of body composition, diabetes or cardiovascular pathologies^{1 5 7 44-46}. The latter has become one of the most important public health challenges of the future. Obesity is also a prime example of complex interactions between environmental, life-style, and endogenous factors that ultimately result in a range of chronic diseases. Preliminary evidence from studies in adults and children indicate that obesity may amplify the adverse effects of ambient air pollution, possibly partly explained by a concomitant role of oxidative stress and systemic inflammation induced or amplified by both factors^{32 47-50}. If verified, a further consequence of the current global obesity epidemic, despite the efforts to improve ambient air pollution, might be remaining or even increasing adverse effects of air pollution on health

The investigation of such complex interactions between time periods and exposures is a formidable challenge. While birth and pregnancy cohorts are considered a key tool to understand early life causes of childhood diseases, these studies take very long time to address effects that may appear much later in life. In contrast, adult cohorts usually lack the relevant information of early life periods. The SAPALDIA cohort off spring offer the unique opportunity to bridge life time periods and to combine information of the past and parent

related health data with the development of health and disease during early life and childhood.

Thus, we plan to initiate a SAPALDIA-off-spring study to investigate the early impact and complex interactions of environmental, life-style and endogenous exposures which lead to the development of cardio-respiratory diseases.

2. Research question:

We hypothesize that exposure to ambient air pollution characterized by fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂) leads to increased respiratory disease and accelerates atherogenesis throughout life including childhood. Thus, early life exposure to ambient air pollution affects lung function and coronary intima-media thickness (CIMT) in adolescents. Based on a model of interrelated pulmonary, systemic, and arterial inflammatory mechanisms, I assume lower lung function, high CRP, and overweight to amplify the association between air pollution and respective health outcomes.

- Hypothesis 1:

Early life and childhood exposure to ambient air pollution is associated with thicker carotid artery walls as measured by CIMT and with lower lung function as measured by spirometry in adolescence.

- Hypothesis 2:

The association between ambient air pollution and CIMT is stronger among adolescents with a: low lung function, b: higher CRP and c: higher body weight.

To investigate the early impact and complex interactions of environmental, life-style and endogenous exposures on respiratory and cardiovascular health, we plan a two step approach. A first investigation, to take place in 2010, will study the interrelations of lung function, CIMT, as a marker of atherosclerosis, systemic inflammation and body weight in off-spring of SAPALDIA participants. Thereby increasing the understanding of the interrelated systemic and organ response to pro-inflammatory environmental exposures, such as air pollution.

The specific role of air pollution, which will require a larger study population, will be studied in a second investigation planned for 2011.

- Off-spring study I

The first study will have two main aims:

- Investigate cross sectional associations between CIMT and lung function with body weight and systemic inflammation markers in adolescence.
- Address questions of recruitment of off-spring, willingness to give blood samples and test measurement protocols of CIMT and lung function in off-spring for study 2.

The recruitment of participants, during the first half of 2010, will be limited to German speaking SAPALDIA study centers. The study aims to recruit approximately 150 off-spring born between SAPALDIA I and SAPALDIA II. Thus, in 2010 the participants will be between 10 and 20 years of age. These children and adolescents will undergo well established clinical assessments of respiratory and cardiovascular health, including blood sampling, and parents will answer respective questionnaires. Recall information on birth weight and height and major birth events can be confirmed by linkage with the national birth statistics.

- Off-spring study II:

The second study aims to investigate:

- the impact of early life and life-time exposure to air-pollution on atherogenesis and respiratory health in adolescents measured by CIMT and spirometry respectively.

This study will invite all off-spring of SAPALDIA participants born between SAPALDIA I and SAPALDIA II (N ~ 1500). Based on the results of study I these children will undergo a clinical assessment of respiratory and cardiovascular health and parents and children will answer respective questionnaires. SAPALDIA offers the unique opportunity to establish the complete personal history of exposure to ambient air pollution from various sources, including exposure during well specified time windows such as pregnancy trimesters and the first months and years of life. The spatial air pollution models developed by the SAPALDIA team and successfully applied in several prime publications in adults will serve as a unique and unprecedented tool to reconstruct life-time exposure and to link children's exposure with the environmental, genetic, and health history of the parent (SAPALDIA participant).

A second study proposal, building on the results of study, will then be submitted in 2011. Apart from the SNF other competitive funding agencies, including the Health Effects Institute and NIH may be approached. The unique strength of the design and existing data of the SAPALDIA parent generation make this a highly promising undertaken.

II. Timeline of study I

October 2008 – April 2009 Preparation of off-spring study I:

- A: Literature search and work up
- B: Co-ordination with ECRHS early life working group
(next meeting 4. Oct. 2008)
Contact with clinical specialists - pediatric pulmonologists and cardiologists
- C: Planning and organization of off-spring study I
Coordinating of offspring study I with organisation of SAP 3
- D: Development of recruitment strategy

Mai 2009 – July 2009 Writing of proposal

- E: Write SNF proposal (Marie Heim Vögtlin Stipendium) -
Submission date 1st of August 2009 (has been changed from April to August only in August this year!)

July 2009 – December 2009 Development of study instruments

- F: Development of questionnaires
- G: preparing recruitment strategy (mailings, participants' information)

January 2010 – July 2010: Start of study I

- H: Recruitment of participants
- I: Data collection of study 1 of SAPALDIA off-spring study

July 2010 – December 2010: Data analyses

- J: Data cleaning and data analyses
- K: Publication of results

II. Main applicant and project team

Within the frame of current SNF grant: 33CSCO-108796, the principal investigator for this nested project is:

Dr Christian Schindler, Institut für Sozial und Präventivmedizin, Universität Basel.

Based on this nested project, Dr Julia Dratva is to head and to submit the proposal as a separate project to the SNF, as main applicant in 2009.

The project team will further include :

Nino Kuenzli	(scientific advisor)
Denise Felber	(coordinator of SAP 3)
Christian Schindler	(statistics)
Sally Liu	(exposure)
Elisabeth Zemp	(gender)

Pediatric specialists will be invited to join the project team as external advisors.

The main applicant, Julia Dratva, is member of the research unit "Women's and gender health" headed by Elisabeth Zemp at the ISPM in Basel. She has been working with SAPALDIA data since 2005, having conducted analysis on the association of menopausal hormone therapy and asthma related symptoms for E. Zemp and on female reproductive characteristics in the SAPALDIA data, as well as the combined data sets of ECRHS and SAPLADIA^{51 52}. She is currently submitting a paper on noise annoyance and quality of life in the SAPALDIA cohort. Other papers and reports focused on infant and childhood health from varying perspectives (feeding, general health, social inequality)⁵³⁻⁵⁹

IV. Budget and required funding for preparational phase of study I

The present application for funding concerns the part I – off-spring study I only.

SAPALDIA 3 planning and organization is under way. To profit from the synergies and ensure necessary data in SAPALDIA 3 needed for the off-spring, we will start the preparation of study I simultaneously. Study I will be able to use equipment, study centers and personal of SAPALDIA 3 thereby reducing the costs and guaranteeing a high quality of data collection. The proposed area of research will require in depth literature study, especially with regard to the specific pediatric issues and the new techniques to be implemented. Further, new study instruments will have to be developed and recruitment strategies decided upon. There is a large interest in working together with the ECRHS early life group and Swiss pediatric specialists, to ensure the international and local acceptance of our study; and these contacts are to be further expanded, respectively initiated.

We therefore apply for a partial funding of this first study phase from October 2008 – July 2009 (20% working time over 10 months = 21'932 CHF) and additional costs for traveling to ECRHS meetings or congresses (2 flights approx. 800 CHF, and accommodation approx 750 CHF). The overall amount totals to 23'482 CHF.

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