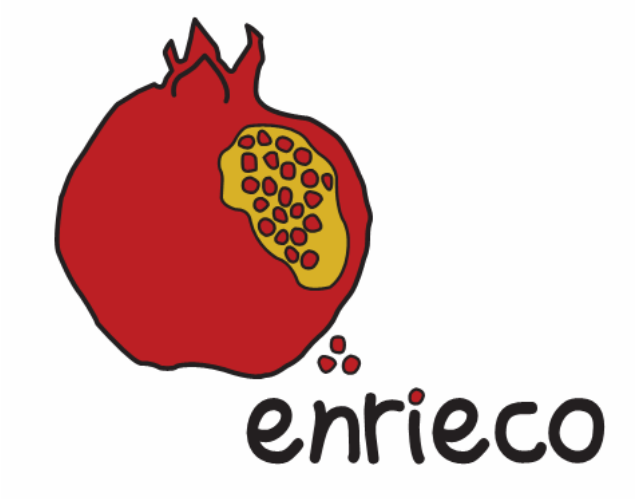
ENRIECO EU project



Work package 5
Deliverable 7

Thomas Keil

Cynthia Hohmann

Institute for Social Medicine, Epidemiology and Health Economics
Charité University Medical Center Berlin, Germany

20 July 2009

Content

1 Introduction 3
1.1 Background 4
1.1.1 Dampness/mould 4
1.1.2 Tobacco smoke exposure 4
2 Case Study of Working Group 1 - Dampness 5
2.1 Analysis plan 5
2.2 Variable definition 6
2.2.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms 6
2.2.2 Exposure: Dampness and mould exposure (birth up to 10-12y) 7
2.2.3 Potential confounding factors and effect modifiers 7
2.3 Agreement plan 7
2.3.1 Key responsibilities 7
2.3.2 Responsibilities of partners 8
2.3.3 Data management and common analyses 8
2.3.4 Publication policy 8
3 Case Study of Working Group 2 – Tobacco Smoke Exposure and Asthma 9
3.1 Analysis plan 9
3.2 Variable definition 10
3.2.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms 10
3.2.2 Exposure: Foetal tobacco smoke exposure 10
3.2.3 Potential confounding factors and effect modifiers 11
3.3 Agreement plan 11
3.3.1 Key responsibilities 11
3.3.2 Responsibilities of partners 12
3.3.3 Data management and common analyses 12
3.3.4 Publication policy 12
4 Case Study of Working Group 3 – Tobacco Smoke Exposure and Wheeze 13
4.1 Analysis plan 13
4.2 Variable definition 14
4.2.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms 14
4.2.2 Exposure: Foetal tobacco smoke exposure 14
4.2.3 Potential confounding factors and effect modifiers 15
4.3 Agreement plan 15
4.3.1 Key responsibilities 15
4.3.2 Responsibilities of partners 16
4.3.3 Data management and common analyses 16
4.3.4 Publication policy 16

ENRIECO WP5 - Deliverable Number 7

Protocol for indoor exposures (ETS and dampness) and allergy and asthma case study

Thomas Keil and Cynthia Hohmann
cynthia.hohmann@charite.de

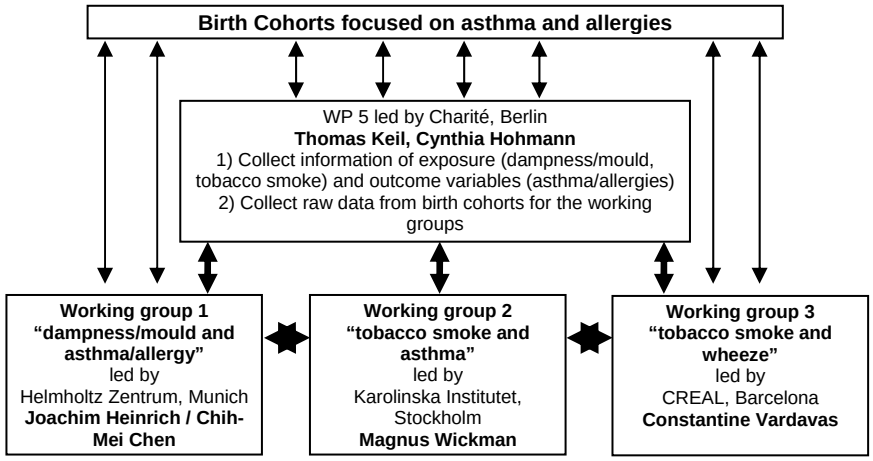
1 Introduction

Work package 5 aims to examine associations between indoor environmental exposures (a. dampness/mould; b. tobacco smoke) and asthma and allergies in children.
These are the most common chronic diseases in childhood and occur from infancy to adulthood. Yet there is still uncertainty about the causes of the high and rising prevalence of asthma/allergies, particularly in industrialised countries. Genes, environment, lifestyle and interactions between those factors are possible explanations.
Indoor environmental exposure is particularly relevant for children in the first two years. Most of our knowledge on indoor exposure and asthma/allergies comes from cross-sectional studies. This emphasises the need for data from long-term birth cohort studies.

Previous case studies in the Global Allergy and Asthma European Network (GA^2LEN) showed that combined analyses with individual participant data from birth cohorts are possible. Data collection, data management and harmonising of variables are laborious and time consuming, and trust building and transparency are the main principles for successful work. Therefore it is important to consider that:

- ⇒ a clear analysis plan, which everyone agrees on, exists from the beginning;
- ⇒ leadership of individual projects and authorship order on the corresponding publication are decided beforehand;
- ⇒ regular updates of analysis status are made;
- ⇒ preliminary results are discussed in person (e.g. face-to-face at airport meetings or telephone conferences) before performing final analyses.

Figure 1. Organisational Structure of WP5



1.1 Background

1.1.1 Dampness/mould

Exposure to a damp indoor environment and mould components has been associated with respiratory health. Exposure to visible mould was reported as a risk factor for childhood wheezing symptoms and asthma. Mould spores seem to play a role for the onset of allergic respiratory symptoms and allergic sensitisation to inhalant allergens. Whether it is appropriate to use mould components such as (1->3)-ß-D-glucan or Extracellular Polysaccharides (EPS) as appropriate markers for mould exposure is under discussion. There are also some studies which showed inverse relationships between high exposure to mould component (1->3)-ß-D-glucan and the risk of wheezing and allergic sensitisation in children. As there are conflicting study results on the health effect of mould exposure and exposure to mould components, we think there is a strong need for further research on the association between mould exposure and allergic outcomes in birth cohort studies. The longitudinal nature of the birth cohort studies gives a clearer direction of causality. The early exposure measurement minimises recall bias and captures the crucial time in immune development. We aim to provide a reliable quantitative summary of the health effect due to exposure to damp indoor environment in European birth cohort studies. As this will be a Europe-wide study, the impact on political decisions will be higher than on a national level.

1.1.2 Tobacco smoke exposure

From the time of conception, the foetus of smoking women is exposed to similar levels of nicotine as an active smoker. Nicotine affects the utero-placental flow and causes impaired foetal nutrition and intrauterine growth retardation. As a part of this effect foetal lung development is impaired, this is

reflected in lowered spirometric flows in the neonate, especially when there is a family history of asthma and hypertension during pregnancy. Epidemiological studies indicate that *in utero* exposure to maternal smoking is a determinant of childhood wheezing. This effect is independent of postnatal exposure to second hand smoke exposure (SHSE) in some, but not all studies. In the Swedish BAMSE cohort it has been shown that *in utero* exposure to maternal smoking was associated with an increased risk of recurrent wheezing and doctor's diagnosed asthma during the first two years of life. In the present case study we aim to provide a meta-analysis approach of the health effect due to exposure to foetal tobacco smoke exposure in European birth cohort studies.

2 Case Study of Working Group 1 - Dampness

Project: Case study on dampness and the association with asthma and allergy in European birth cohorts

Chen-Chih Mey, Joachim Heinrich and Christina Tischler
chih-mei.chen@helmholtz-muenchen.de

Participating birth cohorts (from the ENRIECO workshop meeting and from GA²LEN):
The Netherlands: KOALA, PIAMA-NHS, Generation R; Sweden: BAMSE; Germany: MAS, GINIplus, LISA; Spain: AMICS-Menorca; UK: Isle of Wight, Leicester 1998, ALSPAC; Denmark: DARC; Italy: NINFEA; C.O.N.E.R.

Time schedule:

1. Data collection	June–October 09
2. Data management / preparation	August–Dec 09
3. Analyses	January–July 10
4. First draft paper	September 10
5. Finalised report	November 10
6. Paper submitted	February 11

Data management:
Raw variables in SPSS or SAS (clearly labelled in English) to be sent to Cynthia Hohmann, data manager, (cynthia.hohmann@charite.de), in Berlin.

2.1 Analysis plan

Analyses:

- bivariate ("univariate"), pooled and separately for each study
- multiple logistic regression analyses, pooled and separately for each study
- optionally: stratified analyses (stratified by parental allergy status, damp homes)
- sensitivity analyses: with/without cohorts that (i) do not have all confounder variables; (ii) used different recruitment procedures, etc
- meta-analyses (if pooling is not reasonable e.g. number of confounding variables differs among cohorts)

Some possible limitations:

- importance of the location of the moisture damage: for "mould spots in **any** room": Possibly different type and amount of exposure (e.g. mould spots in living room vs. bathroom)
- mould spots: only viable fungi, non-viable fungal components and its effects are not considered (such as ß-D-glucan or EPS)
- it will be difficult to determine the effect of exposure to mould from children who have moved several times during their childhood as the variation of the exposure may be very big.
- possible bias of the questionnaire-based exposure assessment.
- the health outcomes are defined slightly differently between the birth cohorts.
- not able to capture the confounding effect as some of the cohorts may not have some of the potential confounders.

2.2 Variable definition

How are outcome and exposure defined?
The definition of all outcome and exposure variables will be decided after assessing which variables are available from the participating cohorts and before final analysis. Each PI will then have to confirm the definition based on the variables of his/her birth cohort.

2.2.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms

Asthma (persistent, late onset) 2 yrs up to age 12 yrs

Definition of "asthma" = if at least 2 out of the 3 following criteria are met:

- doctor ever diagnosed asthma
- wheezing → **birth up to 12 yrs**
- asthma medication

Allergic rhinitis 2 yrs up to age 12 yrs

- doctor ever diagnosed allergic rhinitis
- doctor ever diagnosed hay fever
- red eyes and/or sneezing without a cold

Allergic eczema birth up to age 12 yrs

- doctor ever diagnosed eczema
- itchy rash
- how long did the itchy skin rash last?
- is there any flexural involvement of the itchy skin rash?

Specific IgE reaction / SPT results birth up to 12 yrs

- Total IgE reaction
- IgE reaction to SX1 or to common outdoor and indoor inhalant allergens
- IgE reaction to mould allergens
- SPT reaction specific to SX1 or to common outdoor and indoor inhalant allergens

- SPT reaction specific to mould allergens

2.2.2 Exposure: Dampness and mould exposure (birth up to 10-12y)

- Visible mould in any room (or specified) except on food
- Damp or wet spots in any room
- Self assessment: dwelling considered as damp
- Condensed water

2.2.3 Potential confounding factors and effect modifiers

Adjustment for possible influencing factors (confounders and effect modifiers)

1. Birth weight
2. Gestational age
3. Mode of delivery
4. Family history of asthma, AR, E (parents)
5. Family history of asthma, AR, E (siblings)
6. Siblings at birth of child
7. Educational level of mother at birth of child (years in education)
8. Educational level of father at birth of child (years in education)
9. Breast feeding duration (in months)
10. Pets (birth to current situation)
11. Sex
12. Day care first attendance
13. Bedroom sharing
14. Humidifier use
15. Heating conditions
16. Seasonality of the birth of the child
17. Seasonality of the questionnaire survey
18. Study centre
19. Move to another house
20. Measured other indoor allergens, such as house dust mites and cats.

2.3 Agreement plan

2.3.1 Key responsibilities

Joachim Heinrich (Helmholtz Zentrum Munich (**HMGU**), Germany) is the leader of this project and has the overall responsibility for all activities

- **Joachim Heinrich** (HMGU Munich, Germany), Thomas Keil (Charité, Berlin, Germany), and Magnus Wickman (Karolinska, Stockholm, Sweden) will take the primary leadership of the research questions with data from GA^{2}LEN birth cohorts. Joachim Heinrich, Chih-Mei Chen and Christina Tischer (HMGU, Munich, Germany) together with Thomas Keil, Cynthia Hohmann and Magnus Wickman will have the major responsibility of manuscript production.

Their tasks include responsibility and guidance for:

- developing an analysis strategy
- informing all partners on a regular basis about the progress of the analyses

- producing a manuscript for publication by Joachim Heinrich, Thomas Keil, Chih-Mei Chen and Cynthia Hohmann; first author Christina Tischer

Thomas Keil and Cynthia Hohmann will be responsible for preparation of datasets and actual pooling of data. Christina Tischer and Chih-Mei Chen will be responsible for data analysis. Interpretation of data is a joint responsibility of the three research groups. All mentioned researchers will participate in the process of the manuscript.

2.3.2 Responsibilities of partners

a. Before sending data for the planned common analyses, each partner is responsible for ensuring that this is in accordance with the national/local data protection laws.
b. All partners are responsible for having datasets prepared as suggested in the proposal of the project.

2.3.3 Data management and common analyses

The partners agree that the **Charité, Berlin, Germany,** will prepare a dataset to allow for statistical analysis at **Helmholtz Zentrum Munich, Germany**, regarding the research question as specified by the three partners. **Thomas Keil, Charité, Berlin, Germany** will be the responsible person from this institute for the whole process of data management. **Chih-Mei Chen and Christina Tischer, HMGU, Munich, Germany** will be responsible for all statistical analyses together with **Thomas Keil and Cynthia Hohmann**. **All other researchers including Joachim Heinrich**, may be involved at different stages in the process of pooling data, performing analyses, interpretation of data, writing summaries of the results for the reports and/or manuscripts as needed.
HMGU, Munich, Germany **is not allowed to perform any other analyses than the ones agreed upon by the partners, or to pass any data or results on to a third party. All possible security measures (e.g. password protected database) will be taken.** Furthermore, for future revisions and to aid transparency, it is mandatory to document each step of the analyses so that data can be reproduced in the future when needed.

2.3.4 Publication policy

All publications or presentations of the results of the common analyses (abstracts, posters, oral presentations, etc.) must be approved by all participating partners. The authorship and the order of authors for publications will be made by a joint decision of all partners and must be in accordance with the ethical considerations in the conduct and reporting of research as stated by the International Committee of Medical Journal Editors (http://www.icmje.org/#author). In the first paper we suggest the order of authors as follows: **Chih-Mei Chen, Christina Tischer and Cynthia Hohmann followed by birth cohort partners involved (2 slots per cohort), Magnus Wickman, Thomas Keil and Joachim Heinrich.**

I agree with all aspects of this document:

Last name	First name	Birth cohort	Date of signature	Signature
Wickman	Magnus	BAMSE		
Keil	Thomas	MAS		
Heinrich	Joachim	GINIplus/LISA		
…	…	…		
…	…	…		

3 Case Study of Working Group 2 – Tobacco Smoke Exposure and Asthma

Project: Case study on foetal tobacco smoke exposure and asthma among 4-6 year olds

Magnus Wickmann
Magnus.Wickman@ki.se

Participating birth cohorts (from the ENRIECO workshop meeting and from GA²LEN):
The Netherlands: KOALA, PIAMA-NHS, Generation R; Sweden: BAMSE; Germany: MAS, GINIplus, LISA; Spain: AMICS-Menorca; UK: Isle of Wight, Leicester 1998, ALSPAC; Denmark: DARC; Italy: NINFEA

Time schedule:

1. Data collection	June–October 09
2. Data management / preparation	August–Dec 09
3. Analyses	January–July 10
4. First draft paper	September 10
5. Finalised report	November 10
6. Paper submitted	February 11

Data management:
Raw variables in SPSS or SAS (clearly labelled in English) to be sent to Cynthia Hohmann, data manager, (cynthia.hohmann@charite.de), in Berlin.

3.1 Analysis plan

Analyses:

- bivariate ("univariate"), pooled and separately for each study
- multiple logistic regression analyses (interaction terms: e.g. indoor dampness x foetal tobacco smoke exposure (FTSE), pooled and separately for each study
- dose response
- optionally: stratified analyses (stratified by secondary smoke exposure, parental allergy status, gender, co-morbidity)
- sensitivity analyses: with/without cohorts that (i) do not have all confounder variables; (ii) used different recruitment procedures, etc

- meta-analyses (if pooling is not reasonable e.g. number of confounding variables differs among cohorts)

Some possible limitations:

- having data on active smoking of the mother, but not on second hand smoke during all three trimesters
- having sufficiently large "clean groups" e.g. mothers who have smoked during any period of pregnancy, but not thereafter compared to
  - mothers who have not smoked during any period of pregnancy, but after pregnancy only
  - mothers with smoking neither during pregnancy nor afterwards
- lack of information on "other" household secondary smoke after birth including paternal secondary

3.2 Variable definition

How are outcome and exposure defined?

The definition of all outcome and exposure variables will be decided **after** assessing which variables are available from the participating cohorts and **before** the final analysis. Each PI will then have to confirm the definition based on the variables of his/her birth cohort.

3.2.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms

Asthma (persistent, late onset) up to age 4-6 yrs

Definition of "asthma" = if at least 2 out of the 3 following criteria are met:

- doctor ever diagnosed asthma (available in all studies)
- wheezing, (ISAAC core question, if available)
- asthma medication (at least some information available in MAS, ECA, BAMSE, PIAMA-NHS, GINIplus, LISA (probable), DARC, Leicester: no info)

Use variables from last time point available at age window 4-6 years. Studies: IoW, MAS, BAMSE, PIAMA-NHS; GINIplus, LISA, Leicester 1998, AMICS Menorca. To be completed.

3.2.2 Exposure: Foetal tobacco smoke exposure

Exposure of interest: foetal tobacco smoke exposure (maternal direct smoking during pregnancy and if possible maternal secondary smoking during pregnancy)

Type of maternal smoking during pregnancy, divided into trimesters and during any period of the first 6 months of the infant's life (if available)

1. Any maternal daily smoking of cigarettes or equivalent
2. Daily maternal smoking
   - 1-4 cig
   - 5-9 cig
   - $\geq$10 cig

3. Any paternal daily smoking of cigarettes or equivalent during pregnancy

4. Daily paternal smoking
   - 1-4 cig
   - 5-9 cig
   - ≥10 cig

5. Other household member daily smoking of cigarettes or equivalent during pregnancy
6. Daily other household member smoking
   - 1-4 cig
   - 5-9 cig
   - ≥10 cig

Time of exposure (2 time periods approach):

1. during any time of pregnancy (data from all three trimesters)
2. during the first 6 months of life

3.2.3 Potential confounding factors and effect modifiers

Adjustment for possible influencing factors (confounders and effect modifiers)

1. Birth weight
2. Gestational age
3. Mode of delivery
4. Family history of asthma and AR (parents and siblings)
5. Educational level (tertiles according to school years as proxy for SES) at birth of child
6. Siblings at birth of child (therefore only older sibs): yes vs no.
7. Indoor dampness
8. Gender (effect modifier?)
9. Breast feeding duration (in months)
10. Atopic eczema (ever)
11. Rhinitis (ever)
12. "Cohort effects"

Stratification:

Involuntary tobacco smoke exposure during the first 6 months of life.

3.3 Agreement plan

3.3.1 Key responsibilities

Magnus Wickman (Karolinska, Stockholm, Sweden) is the leader of this project and has the overall responsibility for all activities

- **Magnus Wickman** (Karolinska, Stockholm, Sweden), **Thomas Keil** (Charité, Berlin, Germany) and Joachim Heinrich, HMGU, Munich, Germany will take the primary leadership of the research questions with data from GA^{2}LEN birth cohorts (to be identified). Magnus Wickman, Åsa Neuman, Anna Bergström, Göran Pershagen and one additional collaborator/co-author (statistician) together with Thomas Keil, Cynthia Hohmann and Joachim Heinrich will have the major responsibility of manuscript production.

Their tasks include responsibility and guidance for:

- developing an analysis strategy;
- informing all partners on a regular basis about the progress of the analyses;

- producing a manuscript for publication (shared senior authorship) Anna Bergström/Thomas Keil, first author Åsa Neuman.

Thomas Keil and Cynthia Hohmann will be responsible for preparation of datasets and actual pooling of data. Anna Bergström will be responsible for data analysis that will be performed by one additional collaborator/co-author (statistician). Interpretation of data is a joint responsibility of the three research groups. All mentioned researchers will participate in the process of the manuscript.

3.3.2 Responsibilities of partners

a. Before sending data for the planned common analyses, each partner is responsible for ensuring that this is in accordance with the national/local data protection laws.
b. All partners are responsible for having datasets prepared as suggested in the proposal of the project.

3.3.3 Data management and common analyses

The partners agree that the **Charité, Berlin, Germany,** will prepare a dataset to allow for statistical analysis at **Karolinska Institutet, Sweden**, regarding the research question as specified by the three partners. **Thomas Keil, Charité, Berlin, Germany** will be the responsible person from this institute for the whole process of data management. **Anna Bergström, Karolinska Institutet, Stockholm, Sweden** will be responsible for all statistical analyses together with **Åsa Neuman, Magnus Wickman, Göran Pershagen, and one additional collaborator from KI, Thomas Keil and Cynthia Hohmann**. **All other researchers including Göran Pershagen** and **Joachim Heinrich**, may be involved at different stages in the process of pooling data, performing analyses, interpretation of data, writing summaries of the results for the reports and/or manuscripts as needed.

Karolinska Institutet, Stockholm, Sweden is not allowed to perform any other analyses than the ones agreed upon by the partners, or to pass any data or results on to a third party. **All possible security measures (e.g. password protected database) will be taken. Furthermore, for future revisions and to aid transparency, it is mandatory to document each step of the analyses so that data can be reproduced in the future when needed.**

3.3.4 Publication policy

All publications or presentations of the results of the common analyses (abstracts, posters, oral presentations, etc.) must be approved by all participating partners. The authorship and the order of authors for publications will be made by a joint decision of all partners and must be in accordance with the ethical considerations in the conduct and reporting of research as stated by the International Committee of Medical Journal Editors (http://www.icmje.org/#author). In the first paper we suggest the order of authors as follows: **Åsa Neuman, Cynthia Hohmann followed by birth cohort partners involved (2 slots per cohort), Joachim Heinrich, Göran Pershagen, Magnus Wickman, and one additional collaborator from KI, Thomas Keil and Anna Bergström.**

I agree with all aspects of this document:

Last name	First name	Birth cohort	Date of signature	Signature
Wickman	Magnus	BAMSE		
Keil	Thomas	MAS		
Heinrich	Joachim	GINIplus/LISA		
…	…	…		
…	…	…		

3.4 Case Study of Working Group 3 –

Project: Case study on foetal tobacco smoke exposure and wheezing among 0-2 year olds

Several interested cohorts did not meet the inclusion criteria of the outcome assessment (4-6 years). They decided to form a separate working group 2.2 with a similar approach to WG 2.1.

Constantine Vardavas
vardavas@edu.med.uoc.gr

Participating birth cohorts (from the ENRIECO workshop meeting and from GA²LEN) with infants >6 months:
The Netherlands: KOALA, PIAMA-NHS, Generation R; Sweden: BAMSE; Germany: MAS, GINIplus, LISA; Spain: AMICS-Menorca, INMA; UK: Isle of Wight, Leicester 1998, ALSPAC, BIB; Denmark: DARC; Italy: NINFEA; C.O.N.E.R.; Portugal: Generation XXI; Greece: RHEA

Time schedule:

1. Data collection	June–October 09
2. Data management / preparation	August–Dec 09
3. Analyses	January–July 10
4. First draft paper	September 10
5. Finalised report	November 10
6. Paper submitted	February 11

Data management:
Raw variables in SPSS or SAS (clearly labelled in English) to be sent to Cynthia Hohmann, data manager, (cynthia.hohmann@charite.de), in Berlin.

3.5 Analysis plan

Analyses:

- bivariate ("univariate"), pooled and separately for each study
- multiple logistic regression analyses (interaction terms: e.g. indoor dampness x foetal tobacco smoke exposure (FTSE), pooled and separately for each study
- dose response
- optionally: stratified analyses (stratified by secondary smoke exposure, parental allergy status, gender, co-morbidity)
- sensitivity analyses: with/without cohorts that (i) have not all confounder variables; (ii) used different recruitment procedures, etc
- meta-analyses (if pooling is not reasonable e.g. number of confounding variables differs among cohorts)

Some possible limitations:

- to have data on active smoking of the mother, but not on second hand smoke during all three trimesters
- to have sufficiently large "clean groups" e.g. Mothers who have smoked during any period of pregnancy, but not thereafter compared to
  - Mothers who have not smoked during any period of pregnancy, but after pregnancy only
  - Mothers with smoking neither during pregnancy nor afterwards
- lack of information on "other" household secondary smoke after birth including paternal secondary

3.6 Variable definition

The definition of all outcome and exposure variables will be decided **after** assessing which variables are available from the participating cohorts and **before** the final analysis.
Each PI will have to reconfirm the definition and use of the variables of his/her birth cohort.

3.6.1 Primary outcome: Allergic sensitisation and physician diagnosis of atopic diseased and symptoms

Wheezing

- wheezing, (ISAAC core question, if available or parental self report, physician diagnosed)
  Variables will be used from last time point available at age window up to 2 years.

Other relevant outcomes, i.e. respiratory tract infections will be taken into consideration (see confounders).

3.6.2 Exposure: Foetal tobacco smoke exposure

Exposure of interest: foetal tobacco smoke exposure (maternal direct smoking during pregnancy and maternal secondary smoking during pregnancy).

Type of maternal smoking during pregnancy, divided into trimesters and during any period of the first 6 months of the infant (if available)

1. Any maternal daily smoking of cigarettes or equivalent
2. Daily maternal smoking
   - 1-4 cig
   - 5-9 cig
   - ≥10 cig

3. Any paternal daily smoking of cigarettes or equivalent during pregnancy
4. Daily paternal smoking
   - 1-4 cig
   - 5-9 cig
   - ≥10 cig

5. Other household member daily smoking of cigarettes or equivalent during pregnancy
6. Daily other household member smoking
   - 1-4 cig
   - 5-9 cig
   - ≥10 cig

Time of exposure (2 time periods approach):

1. during any time of pregnancy (data from all three trimesters)
2. during the first 6 months of life

3.6.3 Potential confounding factors and effect modifiers

Adjustment for possible influencing factors (confounders and effect modifiers)

1. Birth weight
2. Gestational age
3. Mode of delivery
4. Family history (parents and siblings) of asthma
5. Educational level (tertiles according to school years as proxy for SES) at birth of child
6. Siblings at birth of child (therefore only older sibs): yes vs no.
7. Indoor dampness
8. Gender (effect modifier?)
9. Breast feeding duration (in months)
10. Atopic eczema (ever)
11. Rhinitis between (ever)
12. "Cohort effects"

Stratification:
Involuntary tobacco smoke exposure during the first 6 months of life

3.7 Agreement plan

3.7.1 Key responsibilities

Constantine Vardavas (CREAL, Barcelona, SPAIN) has the overall responsibility for all activities

- **Constantine Vardavas** and **Manolis Kogevinas** (CREAL, Barcelona, SPAIN) and **Thomas Keil** (Charité, Berlin, Germany) will take the primary leadership of the research questions). Constantine Vardavas, Evridiki Patelarou, Mark Niuewenhuijsen and Manolis Kogevinas and one additional collaborator/co-author (statistician) together with Thomas Keil, and Cynthia Hohmann will have the major responsibility of manuscript production.

Their tasks include responsibility and guidance of:

- developing an analysis strategy
- informing all partners on a regular basis about the progress of the analyses
- producing a manuscript for publication (shared senior authorship) Mark Niuwenhuijsen/Manolis Kogevinas, first author Constantine Vardavas

Thomas Keil and Cynthia Hohmann will be responsible for preparation of dataset and actual pooling of data. Constantine Vardavas and Evridiki Patelarou will be responsible for data analysis that will be performed by one additional collaborator/co-author (statistician). Interpretation of data is a joint responsibility of the research group. All mentioned researchers will participate in the process of the manuscript.

3.7.2 Responsibilities of partners

a. Before sending data for the planned common analyses, each partner is responsible to ensure that this is in accordance with the national/local data protection laws.
b. All partners are responsible to have data sets prepared as suggested in the proposal of the project.

3.7.3 Data management and common analyses

The partners agree that the **Charité, Berlin, Germany,** will prepare a dataset to allow for statistical analysis at **CREAL, Spain**, regarding the research question as specified by the three partners. **Thomas Keil, Charité, Berlin, Germany** will be the responsible person from this institute for the whole process of data management. **Constantine Vardavas and Evridiki Patelarou, CREAL, Spain** will be responsible for all statistical analyses together with **one collaborator from CREAL, Thomas Keil and Cynthia Hohmann**. **All other researchers including Mark Niewenhuijsen** and **Manolis Kogevinas** can be involved at different stages in the process of pooling data, performing analyses, interpretation of data, writing summaries of the results for the reports and/or manuscripts when needed.

CREAL, Barcelona Spain is not allowed to perform any other analyses than the ones agreed upon by the partners, or to pass any data or results on to a third party. All possible security measures (e.g. password secured database) will be taken. **Furthermore, for future revisions and to be transparent, it is mandatory to document each step of the analyses so that data can be reproduced in the future when needed.**

3.7.4 Publication policy

All publications or presentations of the results of the common analyses (abstracts, posters, oral presentations, etc.) have to pass the agreement of all participating partners. The authorship and the order of authors for publications will be made by a joint decision of all partners and has to be in accordance with the ethical considerations in the conduct and reporting of research as stated by the International Committee of Medical Journal Editors (http://www.icmje.org/#author). In the first paper we suggest the order of authors as follows: Constantine Vardavas, Cynthia Hohmann, Evridiki

Patelarou, followed by birth cohort partners involved (2 slots per cohort), one additional collaborator from CREAL, Thomas Keil, Mark Nieuwenhuijsen and Manolis Kogevinas.

I agree with all aspects of this document:

Last name	**First name**	**Birth cohort**	**Date of signature**	**Signature**
Vardavas	Constantine	RHEA		
Wickman	Magnus	BAMSE		
Keil	Thomas	MAS		
Heinrich	Joachim	GINIplus/LISA		
…	…	…		