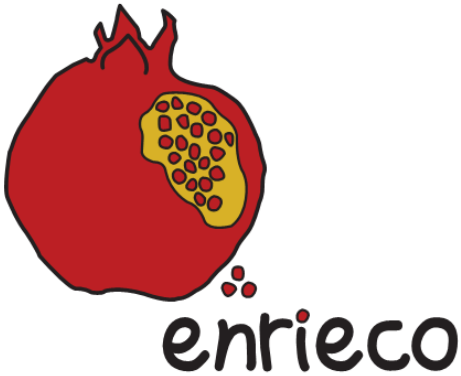
The ENRIECO Project:

ENVIRONMENTAL HEALTH **R**ISKS IN **E**UROPEAN BIRTH **CO**HORTS



ENV-FP7-2008-226285

Deliverable 20

Report

Exposure-Response Relationships for the Case Studies on Indoor Exposure and Allergy and Asthma

Work Package 5

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Deliverable	:	20
Title	:	Exposure-response relationships for the Case studies on Indoor Exposure and Asthma and Allergy
Nature	:	R
Dissemination level	:	PU
Planned	:	Month 21
Actual	:	30 November 2010 (original) 23 February 2011 (revised)

Content

Summary

Work package 5 was to develop a protocol for the construction and evaluation of databases, composed of existing environmental and health data of European birth and pregnancy cohorts. Three case studies were conducted to explore in depth the non-pooled and pooled analyses of existing data, to show the potential of this approach and to explore difficulties. To ease the procedure for each working group, protocols for the execution and evaluation of the planned case studies were prepared.

The protocol for database building and the protocol for the conduction of the case studies were based on experiences from the GA^{2}LEN network and modified by experience gained in ENRIECO. For database building the work package coordinator established and kept going the contact with birth cohort members. The work package coordination collected available variables of different cohort and the individual participant data. Data was harmonized, verified by the cohorts and sent to the working groups.

Working group 1 evaluated the association between exposure to mould and dampness and the risk of allergic disorders in European birth cohort studies. There were 8 out of 11 participating birth cohorts with information on early domestic mould and/or dampness exposure. The aim of working group 2 was to examine foetal second hand tobacco smoke exposure and its association with asthma development in children at age four to six years. Nine European birth cohorts including more than 35 000 children were included. Working group 3 investigated the role of prenatal and postnatal exposure to maternal active smoking and maternal passive smoking on the development of wheezing up to 2 years of age.

In work package 5, it was feasible to calculate combined estimates of environmental health risks using data from 19 European birth cohorts and the cohorts were interested and very committed to this collaborative project of combined data analyses. In the centralized approach, used in this work package, the central storage of data allowed a flexible handling of data and with a single data collection and harmonization process, it was possible to conduct not only one but three combined analyses with different foci.

The centralized approach is recommended for combined analyses addressing variables with very heterogeneous assessments across cohorts where a flexible handling of data is essential and an established basis of trust and work experience between participating partners already exists.

Work Package Coordination

Background

Asthma and allergies are the most common chronic diseases in childhood. They can start in infancy and often last up to adulthood. Yet, there is still uncertainty about the causes of the high and in some regions still rising prevalence, particularly in industrialized countries (1, 2). Genes, environment, lifestyle and interactions between those factors are possible explanations.

Most of our knowledge on indoor exposure and asthma and allergies comes from cross-sectional studies. This emphasizes the need for data from long-term birth cohort studies. The sample sizes of many cohorts may not be sufficient on their own for analyzing certain outcomes and exposures. Harmonizing and combining their data increases statistical power and allows examining rare exposures-response relationships and the comparison of regional differences in Europe.
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.

Three objectives were defined for work package (WP) 5:
(1) WP 5 was to develop a protocol for the construction and evaluation of databases, composed of existing environmental and health data of European birth and pregnancy cohorts. Methods for database building were evaluated, and recommendations for further work were made.
(2) To ease the procedure for each working group (WG), WP 5 prepared protocols for the execution and evaluation of the planned case studies which examined associations between indoor environmental exposures (a. dampness/mould; b. second hand tobacco smoke exposure) and asthma and allergies in children.
(3) Three case studies were conducted to explore the advantages and disadvantages of the non-pooled and pooled analyses of existing data, to show the potential of this approach and to detect and describe difficulties.

Figure 1 displays the working structure of work package 5 (WP5) showing the coordination and communicational processes.
The first and second objectives will be discussed in the following subchapters. The case studies are described in the subsequent WG-reports.

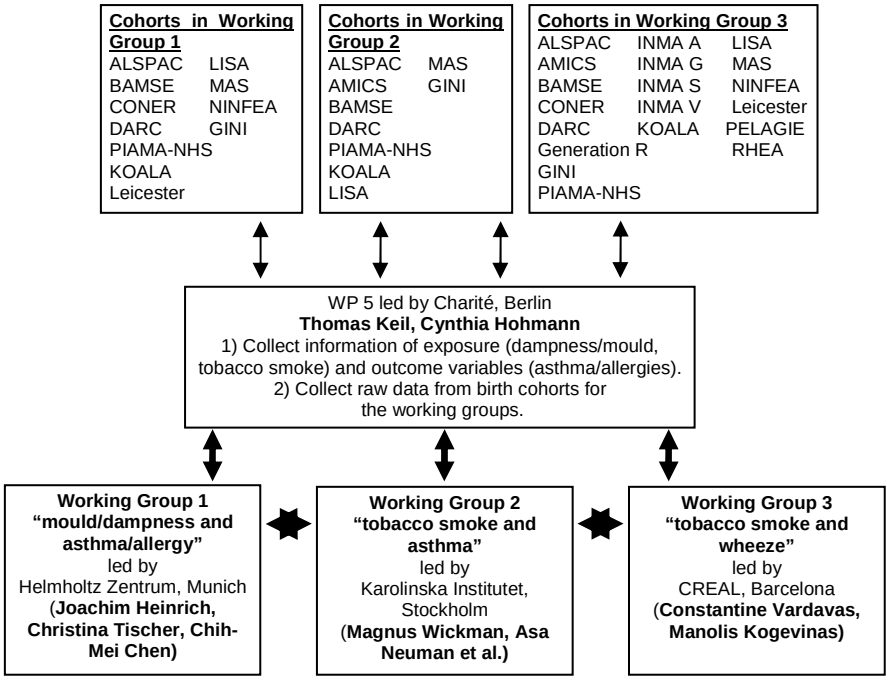


Figure 1. Organizational structure for case studies on mould/dampness and second hand tobacco smoke exposure and wheezing, asthma and allergies.

Methods

The protocol for database building and the protocol for the conduction of the case studies were based on experiences from the birth cohort network in GA^{2}LEN and modified by experience gained in ENRIECO. Working steps were evaluated and guidelines for research groups who are planning further case studies were developed.

Specific methods used for the conduction of the case studies are described each of in the according sections of the working group reports.

Results

Protocol for database building

The process for database building can be divided in two main parts: (1) preparatory steps and (2) database building and analyses.

(1) Preparatory Steps

(I) Definition of Key Responsibilities: Responsibilities for the coordinating process and combining of different birth cohort data has to be clearly defined. While the WP-leader/WP-coordinator is in charge of the coordination processes including the communication with participating birth cohorts and the collection of raw individual participant data, the WGs have the key responsibility for final analysis. Interpretation of data is the joint responsibility of both research groups.

(II) Trust Building and Agreement: Participating cohorts are considered to provide valuable, previously collected and longitudinal data which makes transparency of the data collection and analysis process essential. A personal meeting with interested cohorts is necessary for a general discussion of the project's content. It helps to substantiate the analysis strategy and to elaborate the Analysis Plan and a Memorandum of Understanding (see section 'Protocol for indoor exposures (ETS and dampness) and allergy and asthma case study'). These documents are collected and centrally circulated by the WG-coordination among interested cohorts for final decision on participation.

(2) Database-Building and Analyses

(I) Collection of Wording and Coding of Variables/ Eligibility of Cohorts: Interested cohorts have to provide the WP-coordinator with the precise definition of their birth cohort variables, including answering categories and follow-ups at which data was collected. After receiving this information from all cohorts, the WP-coordinator conducts overviews (see appendix, table 1). These are sent to the PIs of each cohort for verification of correctness and completeness and to the WGs who are to perform later analyses. The WGs are to decide which cohorts are eligible to participate in the planned analyses and which analyses are possible with the available data, respectively.
An overview of the final variable selection is sent to the cohorts with a request to send the corresponding individual participant data.

(II) Collection of Individual Participant Data: Individual participant data, chosen for analysis, is collected by the WP-coordinator. Participating cohorts receive the agreement form (see section 'Protocol for indoor exposures (ETS and dampness) and allergy and asthma case study'), which regulates data access, storage, management, analysis, and publication policy including authorship issues. The initial data management and harmonization of variables is done by the WP-coordinator. The modified cohort datasets are sent to the WGs. Further data management and data analysis are conducted by the WGs.

(III) Check of Completeness and Correctness of Data/ Data Harmonization: The WP-coordinator has to check the complete provision of requested variables and that datasets are correct in terms of variable names, -labels and -values.
The WP-coordinator harmonizes the datasets of different cohorts according to the variables requested by the WGs (e.g. see attachment, table 2). Datasets with identical variable and value labels are prepared for the needs of different working groups. Original dataset and syntaxes used for variable modification have to be saved and provided to the working groups for a later replicability.

(IV) Descriptive Analyses and Data Verification: The WP-coordinator prepares descriptive analyses of each modified dataset. The results are to be sent to the PIs and data managers of the cohorts who have to verify the data. Discrepancies are to be reported to the WP-coordinator and solved in discussion.

(V) Final Analyses and Protocol Writing: The verified data is sent to the WGs. They are to receive: (1) A dataset containing all original and modified variables. By this, the modification process is replicable and variables can be further adapted if needed; (2) A dataset containing modified variables only. It may serve as a shorter and clear working dataset ensuring an easy handling during analyses; (3) The syntax used for data modification and (4) an complete overview of all original variables used for each cohort.

Further description of methods and results for combined data analyses are reported in the working group reports.

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

A protocol was developed for each working group containing information on the analysis and the agreement plan. The preparation of a protocol provided all partners (WP-leader, WP-coordinator, WG-members and contributing cohorts) with transparency of the process. Furthermore, by signing the agreement plan, all partners accept obligations.

In the following, the protocol developed for WG 1 (dampness/mould) is presented. The structure of the protocols for WG 2 and WG 3 were alike with according modifications of partners involved, outcome-exposure variables investigated and planned analyses.

Protocol for working group 1, case study on mould/dampness and asthma and allergy

Key responsibilities

Joachim Heinrich (Helmholtz Zentrum Munich (HMGU), Germany) is the leader of working group 1 and has the overall responsibility.
Joachim Heinrich (HMGU Munich, Germany) and Thomas Keil (Charité, Berlin, Germany), and 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 and Cynthia Hohmann 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 two research groups. All mentioned researchers will participate in the process of the manuscript.

Responsibilities of partners

- 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.
- All partners are responsible for having datasets prepared as suggested in the proposal of the project.

Data management and common analyses

The partners agree that the Charité, Berlin, Germany, will prepare a dataset for the statistical analysis at Helmholtz Zentrum Munich, Germany, regarding the research question as specified by the partners. Thomas Keil and Cynthia Hohmann, 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.

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 (1-2 slots per cohort), Thomas Keil and Joachim Heinrich.

Conclusion

In a centralized approach, applied in WP5, three combined analyses evaluated the effects of indoor environmental exposures on allergic and respiratory diseases. The case studies were used to explore feasibility, potentials and difficulties of harmonizing and merging partly heterogeneous datasets of European pregnancy and birth cohort studies.

A centralized approach for combined analyses was followed in WP5 with a WP-coordinator (WPC) and three WGs analysing allergic outcomes in different age groups. The WPC established and sustained contact with 19 birth cohort study teams and collected information on available variables in each dataset. After the WPC harmonized all relevant variables of individual participant data according to the analysis plan, the cohort study teams were asked for verification. Finally, each of the three WGs received harmonized datasets for combined data analyses.

Recommendation

It was feasible to calculate combined estimates of environmental health risks using data from 19 European birth cohorts and the cohorts were interested and very committed to this collaborative project of combined data analyses. European birth cohorts provide in aggregate a unique research resource that can and should be exploited to obtain added value for research objectives that require large datasets.

Combined analyses help to avoid fragmentation of many individual and possibly inconclusive results by single cohort analyses. Furthermore, results from large cross-cohort analyses may be more likely to be accepted for publication in higher ranked scientific journals.

For the success, several personal meetings with the working groups were necessary to discuss and agree on the final analysis plans. In the centralized approach, used in this work package, the central storage of data allowed a flexible handling of data and with a single data collection and harmonization process, it was possible to conduct not only one but three combined analyses with different foci. Each cohort needed only few resources of personnel, but as a consequence was only little involved in the harmonization and analyses process. For a central storage of data at an external institution, a solid structure of trust and experience had to be established beforehand.

The centralized approach is recommended for combined analyses addressing variables with very heterogeneous assessments across cohorts where a flexible handling of data is essential and an established basis of trust and work experience between participating partners already exists.

It is strongly recommended that resources are carefully planned. At least a kick-off meeting and another 4 meetings should be held. In a centralized approach with data collection and harmonization of up to 19 cohort datasets, resources of a post doc would be needed for 9 months and an additional 2 months should be planned per each analyses and manuscript preparation.

To increase the willingness of birth cohorts to participate in collaborative projects on combined data analyses, financial reimbursement for time and effort to provide previously collected datasets should be considered.

References

(1) Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child 1989; 64(10):1452-1456.

(2) Maziak W, Behrens T, Brasky TM et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. Allergy 2003; 58(7):572-579.

Appendix

Table 1. Exemplary document to check on data availability; variables assessed by different cohorts regarding mould, dampness and wet spots for WG 1.

Study	Variables Definition	Answering Categories	Age
ASLPAC	Is there ever any damp, condensation or mould in your home?	yes / no	8m,1-2y,2-3y,5y, 7y,10y
			8m,1-2y,2-3y,5y, 7y,10y
mold only	'Mould on walls'	yes / no	8m,1-2y,2-3y,5y, 7y,10y
BAMSE	Is there, or has there ever been, any type of moisture damage (damp patch/ mould spots and the like) in the home?	yes / no/ don't know	0-6m
	-Is there, or do you (the inspector) suspect there is, a damage from dampness, mould or rot in the ground construction or ground level of the building	yes / no	2y
(case control)	Do you (the inspector) find a damage from dampness, mould or rot in wet areas, or do you suspect there is such (a hidden) damage? // Possible answers; Yes/ No	yes / no	2y
mould only	Has there been any visible mould/mildew in the home in the past year?	yes / no	0-6m
	Has there been visible mould damage/odour in the home (excluding superficial growth in tile grout/on walls in wet room and the like) since the child turned 4?	no / yes, in the child's room/ yes, in other area	8y
	Has there been visible mould growth or perceptible mould smell in the dwelling?	yes / no	12y
	How old was your child when there was mould growth or mould smell in the dwelling?	younger than 9/ 9-10 years old/ older than 10/ has occurred in the past 12 months	12y
CONER	In the last 6 months, have you noticed wet spots or mould on walls or ceiling in child's bedroom?	yes / no/ I don't know	6m
	Have you noticed wet spots or mould on walls or ceiling in child's bedroom after his six months of life?	yes / no/ I don't know	15m
mould only	Have you noticed mould on walls?	yes / no; in which of the following rooms: kitchen, dining room, parents bedroom, child bedroom, bathroom, other rooms	0
DARC	Are there visible wet spots or mould spots on walls/ ceilings in the…?	bathroom: yes / no; child's sleeping room: yes / no	0-6m, 7-12m, 18 m, 3y, 5y
GINI	Are or were there visible mildew or mould spots on walls (except on food)?	Yes/ no	1y,2y,6y
	Are or were there visible mildew or mould spots on walls (except on food) in each of the following rooms:	Bedroom/child's room/ somewhere else in dwelling/ cellar/ nowhere	10y
KOALA			
mould only	Are there visible mould spots on the walls of the rooms your child is in regularly?	yes / no	1y
LISA	Are there mould or mildew stains in following rooms (except on food)?	Bedroom/child's room/ somewhere else in dwelling/ cellar/ nowhere	6y,10y
	Are there dampness, mildew or mould stains somewhere in the dwelling (except on food?)	yes/no	0,1y,2y,4y
PIAMA-NHS	Did you see any damp stains or mould spots on ceiling or walls in the past 12 months?	yes/ no	3m, 1y, 2y, 3y, 4y, 5y, 6y,

Study	Variables Definition	Answering Categories	Age
	If yes, was it in:	bathroom, living room, child's bedroom, parental bedroom (kitchen)	7y, 8y, 11y 3m, 1y, 2y, 3y, 4y, 5y, 6y, 7y, 8y, 11y (5y, 6y, 7y, 8y, 11y)
Leicester	In your child's bedroom, during the winter months, are there patches of mould or fungus?	yes / no	0,1,2y,3y,4y,5y (again 2-4years later for clinic subsample n=488)
	Please list other rooms in your house affected by mould or fungus.	text	0,1,2y,3y,4y,5y (again 2-4years later for clinic subsample n=488)
NINFEA *mould only*	Did you notice that mould have appeared in your house in the last three months?	yes / no	pregnancy
	Did you notice that mould have appeared in your house during the third trimester of pregnancy?	yes / no	6m
	In the last 6 months, have you noticed mould on the walls or ceiling in the room your child slept most frequently?	yes / no	6m
MAS	Are there spots of mildew or mould in the dwelling your child is living in?	yes / no	9y,10y

Table 2. Variable selection of WG1, exemplary for data harmonization process.

id	Identification number, pseudo-id for every cohort
cohort	Name birth cohort
EXPOSURE	
mould_0, mould_3m, mould_6m, mould_1 mould_1.5, …	***Visible mould/mildew somewhere / child's room*** (table3+4) 1=yes, 0=nein, NA=missing For every age
dampmould_0, dampmould_3m, dampmould_6m, …	***Dampness/moisture/mould stains somewhere / child's room*** (table5+6) 1=yes, 0=nein, NA=missing For every age
HEALTH OUTCOMES	
ddasthma_0, ddasthma_1, …	***Doctor diagnosed asthma ever/last 12 months*** (table 1) 1=yes, 0=no, NA=missing For every age
asthmamed_3, asthmamed_4, …	***Asthma treatment/medication intake*** (table 4) 1=yes, 0=no, NA=missing For every age
wheeze_0, wheeze_1, …	***Ever wheeze/wheezing*** (table 5) 1=yes, 0=no, NA=missing For every age
wheeze12m_0, wheeze12m_1, …	***Wheeze/wheezing in the past 6-12 months*** (table 6) 1=yes, 0=no, NA=missing For every age
eyenose12m_0, eyenose12m_1, …	***Itchy, watery eyes/sneezing, runny, itchy, blocked nose*** (table 7+8) 1=yes, 0=no, NA=missing For every age
ddeczema_0, ddeczema_1, …	***Doctor diagnosed ever atopic (allergic) eczema / atopic (allergic) neurodermitis*** (table 1) 1=yes, 0=no, NA=missing For every age
ddeczema12m_0, ddeczema12m_1, …	***Doctor diagnosed atopic (allergic) eczema / atopic (allergic) neurodermitis in the past 6-12 months*** (table 2) 1=yes, 0=no, NA=missing For every age
sens_inhalant_0, sens_inhalant_1, …	***Sensitisation against inhalant allergens: mite, cat, dog, pollen, trees, mould, grass*** (tables specific IgE) 1=yes, 0=no, NA=missing For every age
CONFOUNDER	
sex	***sex*** 1=male 0=female
birthw	***Birth weight*** Indicate in gram
sibbirth	***Siblings at birth*** Indicate the number
pet_0, pet_1, …	***Pet at home*** 1=yes, 0=no, NA=missing For every age
parallergy	***Parental allergy, neither mother or father ("yes" to neither hay fever, asthma or allergic eczema) -> recode variable*** 1=yes, 0=no, NA=missing
matedu	***Maternal education -> recode into two or three levels***

	1=low, 2=medium, 3=high, NA=missing
matsmoke	***Maternal smoking during pregnancy*** 1=yes, 0=no, NA=missing For every trimester
smoke_0, smoke_1, …	***Smoking at home*** 1=yes, 0=no, NA=missing For every age
heating	***Heating system at home*** 1=inside the dwelling/house, 0=outside the dwelling/central heating, NA=missing For every age
heatingmat	***Heating material used at home*** 1=oil, 2=electric, 3=gas, 4=coal, 5=wood, 6=other, NA=missing For every age

Working Group 1: Dampness/Mould and Asthma and Allergies

Researchers involved: Christina Tischer, Chih-Mei Chen, and Joachim Heinrich

Background

Critical reviews within the past 10 years observed an increased risk of respiratory and allergic health outcomes in children living in a damp and mouldy environment. A European review (NORDDAMP) of studies published prior to 1998 concluded that there is strong evidence for an association between dampness and an increased risk for respiratory and allergic symptoms in children and young adults [1] which was also confirmed in a subsequent review (EUROEXPO) of studies published from 1998 to 2000 [2]. In 2004, the Institute of Medicine (IOM) of the National Academy of Sciences reviewed studies published up to late 2003 and concluded that there is sufficient evidence of an association between exposure to dampness and mould and wheeze in children. Similar was observed for physician-diagnosed asthma or asthma symptoms ([3]). Subsequent studies, not included in the IOM review have strengthened the positive association between home dampness and new-onset asthma in children up to the age of 7 years [4]. Recently, the World Health Organization concluded that there is sufficient epidemiological evidence available to show that exposure to dampness and mould was associated with an increased risk of respiratory symptoms and exacerbation of asthma in children and adults [5].

However, there are only two investigations which provided quantitative summaries of the findings. In a meta-analysis of epidemiologic studies in 2007 [6], exposure to dampness or visible mould at home was significantly positively associated with wheeze in children. Another cross-sectional based collaborative investigation among original studies conducted in Russia, North America and 10 countries in Eastern and Western Europe (PATY) reported highly consistent summary estimates for wheeze, nocturnal cough, sensitivity to inhalant allergens and hay fever when exposed to domestic mould ([7]).

In contrast to the above mentioned investigations, the ENRIECO project (Environmental Health Risks in European Birth Cohorts) is exclusively based on European population-based observational birth cohort studies. The focus of this European collaboration is focused on asthma and allergy in children. To our knowledge, there are only 4 publications on exposure to visible mould and its effect on allergy development in children within the participating 11 birth cohorts up to now.

The objective of this investigation is to assess whether early exposure to dampness and mould is associated with allergic health outcomes during child's respiratory and allergic health development between birth and 10 years of age.

Methods

Birth cohort characteristics

For the ENRIECO investigation, study designs, exposure and outcome assessments of European birth cohort studies were compared. ENRIECO is a project conducted within the European Union's 7th Framework Programme [Theme 6, Environment (Including Climate Change)]. The focus of this collaboration is to investigate specific environment and health causal relationships in pregnancy and early life on the later health development in children. The foetus and infant are especially vulnerable to the exposure to environmental risk factors that disrupt the developmental processes. Therefore, prospective birth cohort studies with similar exposure and health outcome assessment were asked to collaborate in order to improve the knowledge base for environment and health linkages. The present investigation evaluates the association between exposure to domestic mould and dampness and the risk of allergic disorders in European birth cohort studies. In total, 11 birth cohort studies with the suitable information on exposure and health outcomes were included. The cohorts started between 1990 and 2004, including between 330 and 14057 children (**table 1**). Most studies were single-centre studies, except the three German birth cohorts (MAS, LISA and GINI) and the two Dutch birth cohorts (PIAMA and KOALA). Four out of eleven birth cohort studies (GINI, MAS, PIAMA, KOALA) may be considered as enriched with respect to the parental allergy status. All participating birth cohorts have ethical approval from their local review boards.

Definition of primary exposure

The most common exposure type described in the participating birth cohort studies was visible mould in the home, in the child's room and dampness and/or mould, respectively. To achieve a maximum number of studies included in the analysis, we combined the exposure to mould and mould or dampness exposure within the home. In order to ensure early exposure, we focused on the first two years of life. Each study's principal investigator had to assert that all relevant variables were selected from the respective birth cohort study.

Definition of allergic diseases

We identified eight health end points, on the basis of the compatibility and availability across the birth cohort studies. The outcomes selected were "early asthma" (0-2 years), "current asthma" (6-10 years) and "ever asthma" (2-10 years). Asthma definition was based on the GA2LEN definition and defined as satisfying 2 out of 3 conditions: doctor-diagnosed asthma ever, parental-reported wheezing (last 12 months) and asthma medication. Further, early, current and life-time "allergic rhinitis" was defined as having symptoms such as sneezing attacks, runny, blocked and itchy nose and itchy, watery eyes. For five out of eleven studies it was also possible to look at sensitization against inhalant allergens indoor as well as sensitization against mould, based on their serum IgE (Immunoglobulin E) levels between 6 and 8 years.

Definition of potential confounders

Eight variables were considered as eligible confounding factors in adjusted analyses of the individual birth cohorts: 1. sex of child (boy versus girl), 2. Parental atopic status (physician-diagnosed asthma, hay fever or eczema), 3. Educational level of parents at birth (by tertile according to school years as proxy for socio-economic status), 4. Maternal smoking during pregnancy, 5. Child's exposure to environmental tobacco smoke in the first two years of life, 6. Breast feeding during (at least 4 months), 7. Siblings (yes or no) and 8. Early daycare attendance (first 2 years of life).

Statistical analysis

Logistic regression was used to calculate crude odds ratios (OR) to assess the effect of early exposure to mould and dampness on the development of allergic disorders such as asthma, allergic rhinitis and allergic sensitization for each cohort individually. Adjusted ORs were calculated using confounding factors mentioned above and which were available for all birth cohorts including in the respective analysis. To summarize the effect estimates among the participating birth cohort in each analysis, we used random effect models to account for the variability between the different studies. The results are presented as forest plots with central point estimates and confidence intervals (CI) of odds ratios (ORs) and summarize the intensity of increased risk of asthma, allergic rhinitis and allergic sensitization with exposure to domestic visible mould and/or dampness. Significant heterogeneity between the included birth cohort studies was indicated if applicable.

Statistical analyses were performed using the statistical software R, version R 2.9.1 (The R Foundation for Statistical Computing).

Results

Frequency of mould/dampness exposure

There are 8 out of 11 eleven birth cohorts from Europe with information on early domestic mould and/or dampness exposure. Within the first 2 years of life, exposure to domestic mould/dampness ranged from 13% to 53% across 8 European birth cohort studies. PIAMA, ALSPAC and LEICESTER had the largest proportion of exposure to mould and/or dampness at home (**table 1**).

Exposure to visible mould and/or dampness and asthma

Five out of 11 studies had information on exposure to early mould and dampness and asthma in the first two years of life (**table 2**). The crude estimates of the single studies as well as the summary estimate did not report a significant effect on the risk for an early asthma diagnosis. Similar was observed for current asthma and asthma diagnosed at any time point above two years of age. The adjustments did not substantially change the crude effect estimates for early, current or ever asthma. There was significant heterogeneity ($p < 0.05$) between the cohorts for the exposure to visible mould/dampness and asthma at any time point above two years of life in the adjusted model (**table 2)**.

Exposure to visible mould and/or dampness and allergic rhinitis

Five studies on early allergic rhinitis and six studies at later ages were included in this investigation (**table 3**). The combined odds to have allergic rhinitis symptoms were significantly for early exposure and at any time point between age 2 and 10 in adjusted analyses (**1.20 (1.02–1.43)**, **1.08 (0.98–1.20)** and **1.18 (1.05–1.31)**, respectively). For all three models, there was no significant heterogeneity between the cohorts indicated.

Exposure to visible mould and/or dampness and sensitization against inhalant allergens

Only five studies had the appropriate information to model the relationship between exposure to early mould and sensitization against inhalant allergens and mould allergy (IgE). However, there was no significant association observed between exposure to visible mould/dampness and sensitization against inhalant allergens and mould at 6-8 years of age in crude and adjusted analyses. Further, there was no significant heterogeneity between the cohorts.
Forest-plots in **Figure 1** illustrate the adjusted ORs and CIs together with the summary estimate for the association between the investigated exposure-response relationships.

Discussion

Our main findings of the meta-analysis among European birth cohorts indicated that exposure to early visible mould/dampness significantly increases the risk of developing allergic rhinitis in children up to 10 years of. Further, there is a non-significant relation that exposure to domestic visible mould is also a risk factor for developing asthma in the first 10 years of life. However, no association was observed between early exposure to visible mould/dampness and allergic sensitization against inhalant allergens or mould.

To our knowledge, this is the first collaboration investigating the effect of visible mould exposure on allergic health outcomes in birth cohort studies only. Up to know there are only two investigations which provided quantitative summaries on the association between mould and dampness exposure and allergic health outcomes in children. Fisk and colleagues summarized the effect estimates from studies of different design, published between 1989 and 2006 [6]. In 2008, 12 cross-sectional based studies within the Pollution and the Young (PATY) [7] study were combined to perform a pooled analysis on over 58 000 children. Both investigations suggested that dampness and visible mould are associated with a number of respiratory and allergic disorders in children. However, in contrast to the present meta-analysis, the latter investigations did not distinguish between different study designs. Further, the timing of health outcome assessment might be also crucial. Some studies included in previous investigations are too young and there might be amount of children who are not at risk of developing asthma, because the follow-up time was too short and the age of the cohort members was still too young. In order to consider children's health development over a longer time period, we chose three different time points, early, current and life-time prevalence of health outcomes.

This investigation has some strength. First, this meta-analysis is focused on European birth cohort studies only and up to now there are only a few publications on visible mould exposure. Second, the

most important strength of this investigation is the identical analysis of each of the 11 birth cohorts and continuous check of comparability. Further, a prospective study design is still the best approach to assess the relationship between exposure and health outcome, adequately, because the longitudinal design can better assign the direction of causality.

However, along with several strengths this approach has also some weaknesses. The meta-analysis for the relation between early exposure to mould/dampness and early asthma observed an increased risk for children aged up to 2 years. However this positive effect could be masked by uncertainties of the diagnosis in the first two years of life and therefore might be of a transient character. In order to increase the number of participating birth cohort studies, we combined exposure to visible mould and exposure to dampness to exposure to mould/dampness. Although this might be less specific defined exposure, visible mould is considered to be the cause of excessive dampness at home and on the other side exceedingly dampness is often considered to be accompanied by mould.

Another potential source of bias might be different methods of exposure assessment among the single European birth cohorts. The entire participating birth cohort studies relied on the parents to report whether dampness or mould is present. We cannot exclude the possibility of reporting bias for participants or parents with respiratory problems due to a higher awareness which would lead to an overestimation within the original studies.

Although 11 birth cohort studies have information to visible mould or dampness and allergic health outcomes, only eight studies assessed exposure to visible mould/dampness within the first two years of life. After defining common allergic health outcomes, the number of studies was reduced to 4 to 7 suitable investigations for the meta-analysis. Further, not all children might be eligible for recruitment, due to different inclusion or exclusion criteria within the original studies. Therefore, the representativeness of some of the birth cohorts and also the common effect estimate, may pose limitations.

General conclusion and recommendation

Existing birth cohort studies which measured data on mould components should consider evaluating their children over a longer time period. Many of the European followed their children until the first years of life. However, priming of the immune system happens very early in life and health effects may appear later in life. Therefore, a long-term view would be more reliable and informative. This considers especially the younger birth cohorts within our common sample.

To compare different studies in Europe, a standardized exposure assessment would be helpful. We did not distinguish between parental or inspector reported exposure assessment, neither between visible mould and dampness. In order to specify exposure, existing or planned investigations should consider asking for visible mould and dampness separately. Further, mould in the bathroom or living room might have a different impact on children’s health development. This may be a potential source of bias in combined analyses. Therefore, information of where visible mould is located within the home would be helpful.

There is still a growing evidence for an association between visible mould exposure and the incidence of asthma and other allergic disorders such as allergic rhinitis or wheeze in children ([8-12]. The role of the timing of exposure as well as the role of exposures at non-residential addresses such as schools or daycare facilities is unclear and should be a focus of future investigations. More research is needed on factors modifying the association between exposure to domestic visible mould/dampness and allergic disorders to identify susceptible subgroups.

REFERENCES

1. Bornehag, C.G., et al., *Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP).* Indoor Air, 2001. **11**(2): p. 72-86.
2. Bornehag, C.G., et al., *Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects.* Indoor.Air, 2004. **14**(4): p. 243-257.
3. *Institute of Medicine: Damp Indoor Spaces and Health.* 2004.
4. Sahakian, N.M., J.H. Park, and J.M. Cox-Ganser, *Dampness and mold in the indoor environment: implications for asthma.* Immunol.Allergy Clin.North Am., 2008. **28**(3): p. 485-505, vii.
5. WHO, *Dampness and Mould. WHO guidelines for indoor air quality.* 2009.
6. Fisk, W.J., Q. Lei-Gomez, and M.J. Mendell, *Meta-analyses of the associations of respiratory health effects with dampness and mold in homes.* Indoor.Air, 2007. **17**(4): p. 284-296.
7. Antova, T., et al., *Exposure to indoor mould and children's respiratory health in the PATY study.* J.Epidemiol.Community Health, 2008. **62**(8): p. 708-714.
8. Gent, J.F., et al., *Levels of household mold associated with respiratory symptoms in the first year of life in a cohort at risk for asthma.* Environ.Health Perspect., 2002. **110**(12): p. A781-A786.
9. Biagini, J.M., et al., *Environmental risk factors of rhinitis in early infancy.* Pediatr.Allergy Immunol., 2006. **17**(4): p. 278-284.
10. Pekkanen, J., et al., *Moisture damage and childhood asthma: a population-based incident case-control study.* Eur.Respir.J., 2007. **29**(3): p. 509-515.
11. Iossifova, Y.Y., et al., *Mold exposure during infancy as a predictor of potential asthma development.* Ann.Allergy Asthma Immunol., 2009. **102**(2): p. 131-137.
12. Karvonen, A.M., et al., *Confirmed moisture damage at home, respiratory symptoms and atopy in early life: a birth-cohort study.* Pediatrics, 2009. **124**(2): p. e329-e338.

Appendix

Table 1: Description of the birth cohort studies included in the ENRIECO case study

Birth Cohort acronym (key reference)	**City / country**	**First year of recruitment**	**Children recruited (n)**	**Early mould/dampness (0-2 years)**
				% (n / N)
LISA [1]	Multicentre / Germany	1997	**3097**	**37 %** (1084 / 2948)
GINI [2]	Multicentre / Germany	1996	**5991**	**15 %** (143 / 933)
MAS	Multicentre / Germany	1990	**1314**	**no early exposure**
BAMSE	Stockholm / Sweden	1994	**4089**	**28 %** (1004 / 3085)
DARC	Odense / Denmark	1998	**562**	**36 %** (191 / 528)
PIAMA	Multicentre / the Netherlands	1996	**3182**	**55 %** (1736 / 1408)
KOALA	Maastricht / the Netherlands	2001	**2834**	**no early exposure**
ALSPAC	Bristol / U.K.	1991	**14057**	**67 %** (8089 / 11997)
NINFEA	Turin / Italy	2005	**1046**	**no early exposure**
CO.N.ER	Bologna / Italy	2004	**434**	**13 %** (51 / 379)
LEICESTER	Leicester / U.K.	1998	**330**	**19 %** (53 / 281)

1. Heinrich, J., et al., *Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates.* Eur Respir J, 2002. **20**(3): p. 617-23.
2. Filipiak, B., et al., *Farming, rural lifestyle and atopy in adults from southern Germany--results from the MONICA/KORA study Augsburg.* Clin Exp Allergy, 2001. **31**(12): p. 1829-38.

Table 2: Crude and adjusted Odds ratios (OR) and 95% confidence intervals (95% CI) of early exposure to mould and/or dampness (0-2 years) and asthma, by random effect meta-analyses (combined effect) and separately by each cohort.

Birth cohort	**Crude Early asthma (0-2y)**	**Adjusted Early asthma[*] (0-2y)**	**Crude Current asthma (6-10y)**	**Adjusted Current asthma[§] (6-10y)**	**Crude Ever asthma (2-10y)**	**Adjusted Ever asthma[$] (2-10y)**
LISA	DEM	DEM	0.97 (0.64 – 1.45)	0.97 (0.63 – 1.51)	0.92 (0.62 – 1.37)	0.92 (0.60 – 1.43)
GINI	0.79 (0.23 – 2.67)	0.35 (0.05 – 2.73)	2.18 (1.12 – 4.25)	2.76 (1.26 – 6.07)	2.10 (1.09 – 4.07)	2.86 (1.31 – 6.27)
MAS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
BAMSE	1.58 (1.29 – 1.94)	1.46 (1.18-1.82)	1.30 (1.00 – 1.70)	1.25 (0.94 – 1.66)	1.44 (1.19 – 1.74)	1.41 (1.15 – 1.73)
DARC	1.08 (0.71 – 1.66)	0.89 (0.48 – 1.62)	0.72 (0.25 – 2.05)	0.56 (0.14 – 2.26)	0.72 (0.25 – 2.05)	0.56 (0.14 – 2.26)
PIAMA	1.04 (0.72 – 1.61)	1.09 (0.71 – 1.69)	1.04 (0.77 – 1.40)	1.02 (0.72 – 1.44)	0.94 (0.73 – 1.21)	0.93 (0.69 – 1.24)
KOALA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
ALSPAC	n.a.	n.a.	1.32 (1.12 – 1.55)	1.17 (0.89 – 1.55)	1.32 (1.12 – 1.55)	1.17 (0.89 – 1.55)
NINFEA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
CO.N.ER	2.86 (1.39 – 5.89)	2.96 (1.29 – 6.78)	n.a.	n.a.	n.a.	n.a.
LEICESTER	n.a.	n.a.	0.50 (0.16 – 1.50)	DEM	0.50 (0.16 – 1.50)	DEM
Combined effect	**1.35 (0.99 – 1.86)**	**1.29 (0.9 – 1.85)**	**1.19 (0.99 – 1.43)**	**1.17 (0.95 – 1.43)**	**1.17 (0.94 – 1.45)**	**1.18 (0.92 – 1.52)**
Test for homogeneity (p)	p = 0.0419	p = 0.0782	p = 0.1295	p = 0.2101	p = 0.0149	p = 0.0258

DEM = Did not enter the model; n.a. = no early exposure and/or respective health outcome information available

[*] *Adjusted for sex, parental allergy, parental education, smoking during pregnancy, early ETS exposure, breast feeding*

[§] *Adjusted for sex, parental allergy, parental education, early ETS exposure, breast feeding*

[$] *Adjusted for sex, parental allergy, parental education, early ETS exposure, breast feeding*

Table 3: Crude and adjusted Odds ratios (OR) and 95% confidence intervals (95% CI) of early exposure to mould and/or dampness (0-2 years) and allergic rhinitis, by random effect meta-analyses (combined effect) and separately by each cohort.

Birth cohort	**Crude Early allergic rhinitis (0-2y)**	**Adjusted Early allergic rhinitis (0-2y)**	**Crude Current allergic rhinitis (6-10y)**	**Adjusted Current allergic rhinitis (6-10y)**	**Crude Ever allergic rhinitis (2-10y)**	**Adjusted Ever allergic rhinitis (2-10y)**
LISA	1.29 (1.08 – 1.54)	1.36 (1.12 – 1.66)	1.00 (0.82 – 1.22)	0.97 (0.78 – 1.22)	1.05 (0.87 – 1.26)	1.00 (0.82 – 1.23)
GINI	1.10 (0.71 – 1.70)	1.27 (0.74 – 2.18)	1.47 (0.97 – 2.22)	1.45 (0.85 – 2.48)	1.49 (1.00 – 2.22)	1.64 (1.08 – 2.50)
MAS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
BAMSE	n.a.	n.a.	1.24 (0.99 – 1.56)	1.09 (0.86 – 1.40)	1.41 (1.17 – 1.70)	1.33 (1.10 – 1.60)
DARC	0.69 (0.24 – 1.98)	0.26 (0.03 – 2.25)	1.98 (0.63 – 6.24)	2.00 (0.42 – 9.65)	1.98 (0.63 – 6.24)	2.15 (0.66 – 6.94)
PIAMA	1.06 (0.89 – 1.27)	1.07 (0.87 – 1.31)	1.08 (0.93 – 1.26)	1.04 (0.87 – 1.24)	1.13 (0.98 – 1.31)	1.13 (0.97 – 1.31)
KOALA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
ALSPAC	n.a.	n.a.	1.19 (1.07 – 1.33)	1.16 (0.96 – 1.41)	1.18 (1.06 – 1.33)	1.14 (1.00 – 1.30)
NINFEA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
CO.N.ER	1.53 (0.74 – 3.18)	1.26 (0.55 – 2.89)	n.a.	n.a.	n.a.	n.a.
LEICESTER	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Combined effect	**1.17 (1.04 – 1.32)**	**1.20 (1.02 – 1.43)**	**1.15 (1.06 – 1.25)**	**1.08 (0.98 – 1.20)**	**1.20 (1.09 – 1.33)**	**1.18 (1.05 – 1.31)**
Test for homogeneity (p)	p = 0.4212	p = 0.3072	p = 0.3502	p = 0.6528	p = 0.1763	p = 0.174

DEM = Did not enter the model; n.a. = no early exposure and/or respective health outcome information available

[*] *Adjusted for sex of child, parental allergy, parental education, smoking during pregnancy, early ETS exposure, breast feeding*

[§] *Adjusted for sex of child, parental allergy, parental education, smoking during pregnancy, early ETS exposure, breast feeding, early day care*

[$] *Adjusted for sex of child, parental allergy, parental education, smoking during pregnancy, early ETS exposure, breast feeding, early day care*

Table 4: Crude and adjusted Odds ratios (OR) and 95% confidence intervals (95% CI) of early exposure to mould and/or dampness (0-2 years) and sensitization against inhalant allergens (indoor) and mould (IgE), by random effect meta-analyses (combined effect) and separately by each cohort.

Birth cohort	**Crude Sensitization against inhalant allergens (indoor) (IgE) (6-8y)**	**Adjusted[*] Sensitization against inhalant allergens (indoor) (IgE) (6-8y)**	**Crude Sensitization against mould (IgE) (6-8y)**	**Adjusted[$] Sensitization against mould (IgE) (6-8y)**
LISA	1.31 (0.95 – 1.79)	1.49 (1.05 – 2.10)	3.22 (0.80 – 12.94)	3.13 (0.77 – 12.66)
GINI	1.04 (0.55 – 1.96)	0.95 (0.43 – 2.09)	DEM	DEM
MAS	n.a.	n.a.	n.a.	n.a.
BAMSE	0.84 (0.66 – 1.09)	0.77 (0.58 – 1.01)	0.68 (0.34 – 1.37)	0.66 (0.32 – 1.33)
DARC	1.30 (0.65 – 2.61)	1.61 (0.61 – 4.22)	1.11 (0.32 – 3.88)	1.24 (0.34 – 4.55)
PIAMA	1.03 (0.79 – 1.33)	1.08 (0.81 – 1.44)	1.13 (0.54 – 2.34)	1.09 (0.52 – 2.27)
KOALA	n.a.	n.a.	n.a.	n.a.
ALSPAC	n.a.	n.a.	n.a.	n.a.
NINFEA	n.a.	n.a.	n.a.	n.a.
CO.N.ER	n.a.	n.a.	n.a.	n.a.
LEICESTER	n.a.	n.a.	n.a.	n.a.
Combined effect	**1.04 (0.87 – 1.24)**	**1.08 (0.80 – 1.45)**	**1.07 (0.63 – 1.83)**	**1.06 (0.61 – 1.84)**
Test for homogeneity (p)	p = 0.2826	p = 0.0446	p = 0.2616	p = 0.2521

DEM = Did not enter the model; n.a. = no early exposure and/or respective health outcome information available

[*] *Adjusted for sex of child, parental allergy, parental education, breast feeding, early day care*

[$] *Adjusted for* parental allergy, early day care

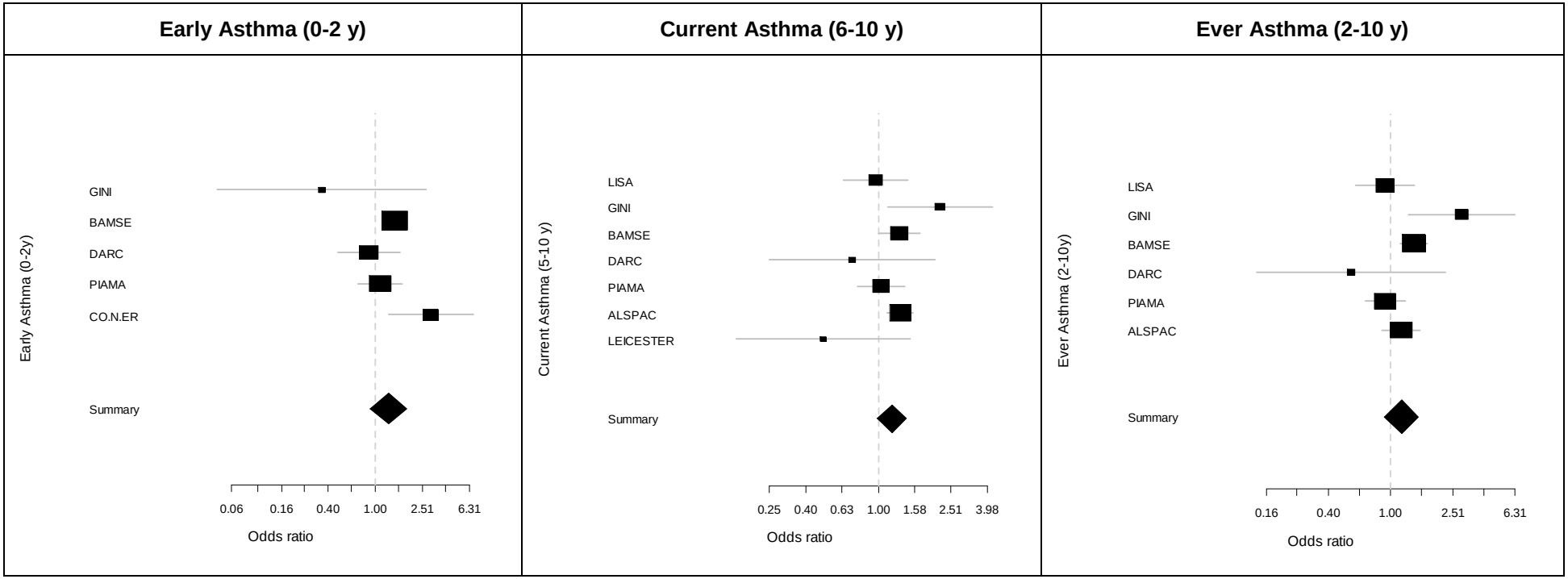


Figure1:

A. Adjusted odds ratios and 95% confidence intervals (95% CI) of exposure to mould in relation to asthma estimated by meta-analyses (combined effect) and separately for each cohort. For each study, the size of the box represents the variance of the individual cohort.

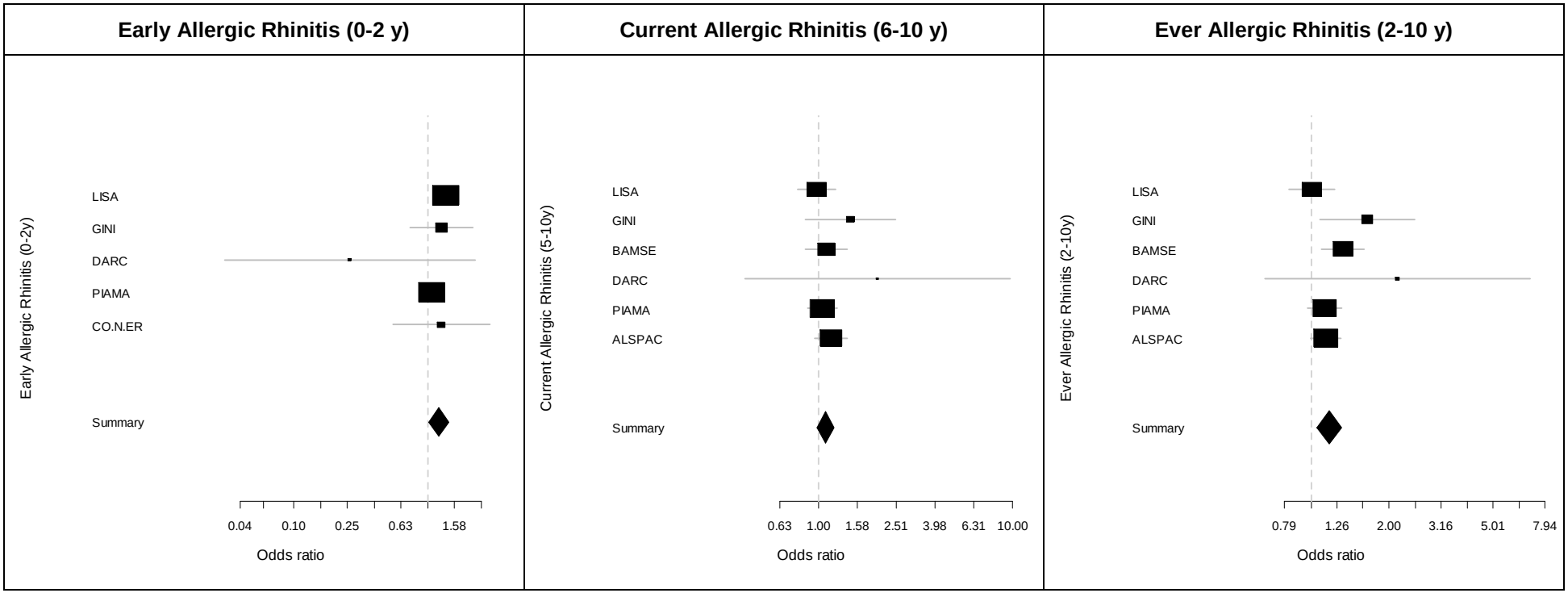


Figure 1:

B. Adjusted odds ratios and 95% confidence intervals (95% CI) of exposure to mould in relation to allergic rhinitis estimated by meta-analyses (combined effect) and separately for each cohort. For each study, the size of the box represents the variance of the individual cohort.

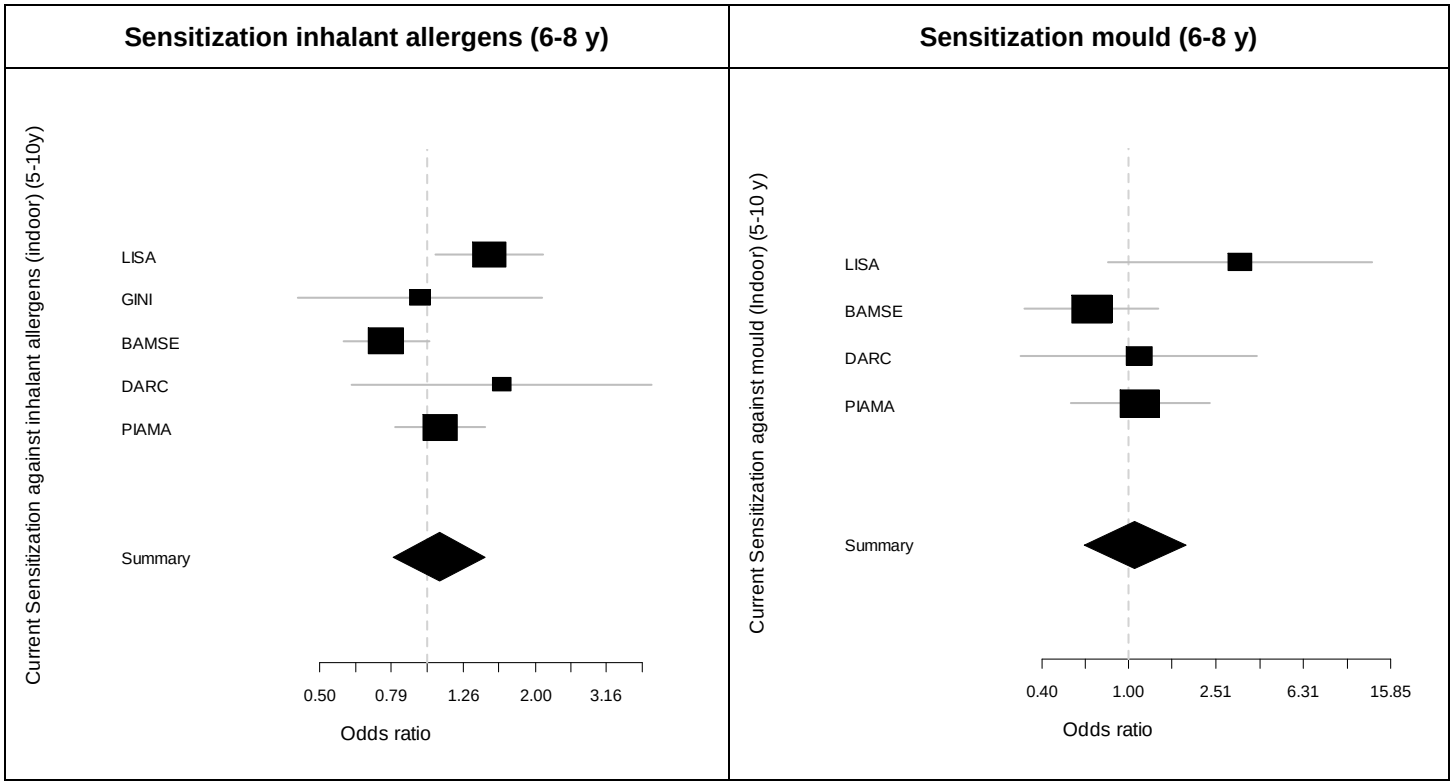


Figure 1:

C. Adjusted odds ratios and 95% confidence intervals (95% CI) of exposure to mould in relation to allergic sensitization estimated by meta-analyses (combined effect) and separately for each cohort. For each study, the size of the box represents the variance of the individual cohort.

Working Group 2: Maternal Smoking during Pregnancy and Wheeze or Asthma at Four to Six Years of Age – Meta-analysis with Individual Participant Data from Eight European Birth Cohorts

Researchers involved: Åsa Neuman, Magnus Wickman, Eva Hallner, Nicola Orsini, Anna Bergström

Background

Adverse effects on children's respiratory health due to tobacco smoke exposure have been reported in several studies and reviews [1-5]. There are critical windows of lung growth and lung maturation in foetal life and in the first years after birth, thus the impact of tobacco smoke exposure is the most hazardous during these periods [6, 7]. Undoubtedly, nicotine, carcinogens and other toxic substances pass the placental barrier affecting the foetus [8-10]. Animal studies have shown decreased foetal lung movements under exposure to tobacco smoke, which might lead to impaired airway development [11]. Mice exposed to tobacco smoke before and shortly after birth have increased airway hyper-responsiveness later in life, measured as altered lung resistance when exposed to metacholine [12]. Changes in substance P nerve fibers of tracheal smooth muscle and increased nerve growth factor levels in the airways were seen in these mice. Thus, the connection between smoke exposure during pregnancy and asthma might be mediated via the development of bronchial hyper-responsiveness [12]. Wheeze is a symptom indicating bronchial hyper-responsiveness and is common among asthmatics [13].

There is some evidence that wheeze, bronchial hyper-responsiveness and impaired lung function in childhood is more strongly associated to intrauterine exposure than to current parental smoking in the home of the child [1, 3, 4, 14-19]. The same is seen for other respiratory health outcomes such as asthma [1, 20]. The challenge for assessing the effect of smoke exposure during pregnancy for airway disease development is to identify a sufficient number of children exposed only during pregnancy, since most pregnant women who smoke continue doing so after delivery. However, some women quit smoking during pregnancy for a number of reasons [21, 22].

The aim of the study was to assess the effect of maternal smoking during pregnancy on asthma and wheeze development in children age four to six years. This study is based on extensive questionnaire data from eight European birth cohorts including children followed prospectively from birth or pregnancy enabling the identification of a sufficient number of children, exposed in foetal life only, for the study of asthma and wheeze development.

Methods

Birth cohort studies

We included European birth cohorts from the ENRIECO collaboration. Inclusion criteria for the meta-analysis were: (i) European population-based observational birth cohort studies focusing on allergy and asthma, with ethical approval from local review boards, (ii) recruitment of new-borns during pregnancy or shortly (i.e. in the first months) after birth, (iii) at least one follow-up assessment of asthma or wheeze outcomes during 4 to 6 years of age, (iv) information on maternal smoking from at least one time point during pregnancy and from the first year after delivery.

Within the ENRIECO project, 47 European pregnancy or birth cohort studies have been identified in which tobacco smoke exposure has been or will be assessed. Twelwe cohorts had data on smoke exposure before and after delivery as well as suitable recruitment periods (follow-up from 4 to 6 years of age). Out of these, ten cohorts provided data to this meta-analysis project. However, two cohorts lacked sufficient outcome data and were therefore excluded. These cohorts were KOALA (The Netherlands) and CO.N.ER (Italy).

In all, eight cohorts were included in this meta-analysis: ALSPAC (UK), AMICS-Menorca (Spain), BAMSE (Sweden), DARC (Denmark), GINI-plus, LISA, MAS (Germany), PIAMA-NHS (The Netherlands). However, GINI-plus (Germany) had insufficient information on maternal smoking in the first year after delivery, and was included only when this information was not required, and ALSPAC (UK) had insufficient data on asthma, thus only current wheeze was assessed as outcome.

The proportions of observations lost to follow-up or with internally missing varied between these eight individual cohorts. In four cohorts, more than 90 % of the children from the original cohort were included. One cohort could include less than 60 % of the children from the original cohort. Consequently, in the meta-analyses, when combining data from all eight cohorts, the number of children included was 22 628, which is almost 70 % of the original cohorts.

Maternal smoking during pregnancy was less common among the children who fulfilled the inclusion criteria compared to all children in the cohorts (19.3 % compared to 22.8 %). Moreover, the included children had parents with significantly higher educational levels (55.9 % compared to 52.7 %) than among all children. In contrast, no differences were seen in wheeze and asthma prevalence among the included children compared to all children in the cohorts.

The meta-analysis was conducted according to the principles expressed in the Declaration of Helsinki. The included birth cohort studies were approved by their local Institutional Review Boards. All participants have provided written informed consent for data collection and analysis.

Definition of outcomes

Current asthma was defined as satisfying at least 2 out of 3 of the following criteria: (i) a doctor's diagnosis of asthma ever; (ii) parental-reported wheezing during the last 12 months according to the International Study of Asthma and Allergy in Childhood (ISAAC) core questions [23]; (iii); asthma medication in the last 12 months.

The time point for outcome assessments was age 5 years, except for BAMSE (Sweden) and ALSPAC (UK) that had available outcome data at age 4 and 6 years, respectively.

Definition of second hand tobacco smoking

Maternal smoking during pregnancy was defined as maternal smoking of at least one cigarette daily during any trimester.
Maternal smoking during the 1st year of life was defined as maternal smoking in the dwelling or near the child during the child's first year of life.
Any smoke exposure during the first year of life was defined as mother, father, partner or other person smoking in the dwelling or near the child during the child's first year of life.

To further evaluate the effect of maternal smoke exposure during pregnancy, maternal smoking during pregnancy and during the first year after delivery was allocated into four categories: (i) no smoking during pregnancy or in the first year (reference category); (ii) maternal smoking during pregnancy only; (iii) maternal smoking in the first year only; (iv) maternal smoking both during pregnancy and during the first year.
Current maternal smoking was defined as mother smoking in the dwelling or near the child at the time of outcome assessment.
Any current smoke exposure was defined as mother, father, partner or other person smoking in the dwelling or near the child at the time of outcome assessment.

Statistical analyses

Study-specific crude and adjusted estimates including dose-response effects were calculated using logistic regression. Results are reported as odds ratios (OR) with 95 % confidence intervals (CI). Different confounder models were tested. The final logistic model included adjustments for sex, parental education as a marker for socio-economy, parental asthma, siblings and birth weight since these covariates resulted in an OR change of more than 5 % or due to subject-matter knowledge. Non-linearity was tested by checking for the best functional and by squaring the model. Confounder sensitivity analysis was done by comparing odds ratios before and after exclusion of missing confounder data. To further exclude the potential effect of current smoking, stratification was done for current maternal smoking and any current smoke exposure at the time of outcome assessment.

The study-specific OR estimates were combined using a random-effects model, which considers both within-study and between-study variation. The meta-analysis results are presented as forest plots with

central point estimates and 95 % confidence intervals of adjusted odds ratios, where the size of the square in the figures represents the variance of the individual cohort. Statistical heterogeneity among studies was evaluated using the χ^2 and I^2 statistics. Sensitivity analysis was performed in which the study with the most deviating OR estimate compared to the other studies was removed to evaluate whether the results were markedly affected by this single study. Such studies were DARC, (Denmark) for wheeze and GINI-plus (Germany) for asthma in Figure 1. In Figure 2, it was DARC (Denmark) for wheeze and AMICS-Menorca (Spain) for asthma.
All statistical analyses were performed with STATA software, version 11, (Stata Corp, College Station, Texas). P<0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of the eight birth cohorts, including the prevalence of maternal smoking during pregnancy, in the first year after delivery and at the time of outcome assessment, as well as wheeze and asthma prevalence at age 4 to 6 years. The prevalence of maternal smoking during pregnancy varied between the different cohorts, from 12.9 % (BAMSE, Sweden) to 37.9 % (AMICS-Menorca, Spain). The prevalence of maternal smoking during the first year of life after delivery ranged from 14.8 % (BAMSE, Sweden) to 38.9 % (MAS, Germany). The highest proportion of smoking mothers was 27.6 % (MAS, Germany), and the lowest 8.8 % (LISA, Germany) when the children were 4 to 6 years of age. The prevalence of wheeze ranged from 5.9 % (DARC, Denmark) to 14.7 % (BAMSE, Sweden). The corresponding proportions for asthma were 3.2 % (LISA, Germany) to 13.7 % (BAMSE, Sweden).

The prevalence of maternal smoking during pregnancy and the first year of the child's life allocated into four disjunctive categories is displayed in Table 2. The majority of the children were not exposed to maternal smoking neither during pregnancy nor in the first year of life. Most of the children exposed to maternal smoking during pregnancy were exposed during the first year after delivery also. However, 724 children were identified who had only been exposed to maternal smoking during pregnancy and not in the first year after birth.

The association between maternal smoking during pregnancy and wheeze and asthma is presented in Table 3. The left panel shows the crude OR for exposure to maternal smoking during pregnancy, irrespective of smoking after delivery. The right panel shows the crude OR for maternal smoking during pregnancy, but not during the first year after delivery, i.e. as described in Table 2.

Figure 1 displays the individual and combined adjusted ORs of maternal smoking during pregnancy on current wheeze and asthma. Two of the cohorts showed a significant association between smoking in pregnancy and wheeze; ALSPAC (UK), adjusted Odds Ratio ($_a$OR) 1.26, 95 % confidence interval (CI) 1.02-1.56, and BAMSE (Sweden), $_a$OR 1.56, CI 1.21-2.02. The combined $_a$OR for wheeze also showed a significant association, $_a$OR 1.27, CI 1.13-1.43. The same was seen for asthma in BAMSE (Sweden), $_a$OR 1.53, CI 1.18-1.98, and MAS (Germany), $_a$OR 2.83, CI 1.29-16.19. The combined $_a$OR

was significant for asthma, $_{a}$OR 1.40, CI 1.10-1.77. No significant heterogeneity was observed between the cohorts for neither wheeze (p=0.738) nor asthma, (p=0.222).

In Figure 2, the individual and combined adjusted ORs of maternal smoking during pregnancy, but not in the first year after delivery, on current wheeze and asthma is displayed. One individual cohort showed a statistically significant association for both outcomes, BAMSE (Sweden), $_{a}$OR 2.17, CI 1.32-3.56, for wheeze, $_{a}$OR 2.02, CI 1.22-3.34, for asthma. The corresponding combined estimates were also significant with $_{a}$OR for wheeze 1.39, CI 1.08-1.78, and asthma 1.56, CI 1.06-2.29. No heterogeneity was observed for neither wheeze, (p=0.540) nor asthma, (p=0.352). Conditioning on any smoke exposure in the first year of life showed similar results. The combined estimate for wheeze was $_{a}$OR 1.50, CI 1.14-1.97, and $_{a}$OR 1.63, CI 1.10-2.40, for asthma.

Stratification for current smoking at the time of outcome assessment was performed to further disentangle the effect of maternal smoking during pregnancy from that of smoking after delivery. This was done for the group of children exposed during pregnancy but not in the first year of life. The combined effect remained significant in the group of current non-smoking mothers with an $_{a}$OR for wheeze 1.56, CI 1.17-2.08, and asthma, $_{a}$OR 1.84, CI 1.24-2.72. Stratification for any current smoke exposure showed similar results, with a combined $_{a}$OR 1.82, CI 1.12-2.49 and $_{a}$OR 1.88, CI 0.99-3.57, for current wheeze and asthma, respectively.

A potential dose-response effect between daily cigarette intake during the first trimester and current wheeze or asthma was done by calculating the difference in adjusted OR for every 5 cigarette increase in daily consumption. Data on amount of cigarettes smoked was available for 7 cohorts (except MAS, Germany). One cohort (DARC, Denmark) reported number of cigarettes smoked during the whole pregnancy, thus this information had to be used. Since one cohort did not have enough data on smoke exposure after delivery (GINI-plus, Germany), 6 cohorts were included in this analysis. For current wheeze, the combined estimate was $_{a}$OR 1.21, CI 1.02-1.43, indicating a positive dose-response effect. The same was seen for asthma, with a combined estimate of $_{a}$OR 1.22, CI 0.99-1.49.

Discussion

This meta-analysis of individual participant data from eight European birth cohorts showed an associated risk between maternal smoking during pregnancy and current wheeze or asthma in preschool age. The large study base allowed us not only to adjust for important potential confounders, but also to exclude the effect of smoke exposure in the first year after delivery as well as at the time of outcome assessments. Additionally, we had available smoke exposure data on other persons near the child besides the mother which allowed for further separation of smoke exposure after birth. Furthermore, dose-response effects were assessed for amount of cigarettes smoked in the 1st trimester and preschool wheeze and asthma. The associated risk for preschool wheeze or asthma in children whose mothers smoked during pregnancy was considerably consistent in all analyses.

Previous studies and reviews have reported an effect of smoking during pregnancy on respiratory disease development [1, 3, 11, 12, 14-19] which is in accordance with our findings. The proportion of mothers smoking only during pregnancy was lower than the proportion smoking both during pregnancy and after delivery, which has been seen previously [15, 21]. Investigating which trimester maternal smoking has the most harmful effect on the fetus regarding respiratory health is difficult, since, despite the fact that most smoking pregnant women smoke throughout the pregnancy, the number of women starting to smoke during the latter trimester are practically non-existent. However, the risk estimates in this study did not change substantially when replacing smoking data from the whole pregnancy with that from the 1st trimester only. This might indicate that the hazardous effects of maternal smoking on the fetal respiratory system presents early in pregnancy. One study has suggested that the harmful effects are not limited to the last 7 weeks of pregnancy since changes in lung function were seen already in preterm infants [24].

We used two ways to assess maternal smoking during pregnancy. In the first model, smoke exposure in the first year after birth was not taken into account. In the second model, we separated the potential effect of early postnatal smoking by excluding the children exposed to tobacco smoke in the first year of life. An associated risk for current wheeze and asthma remained. The point estimate was even higher in the exposure group where exclusion of smoking in the first year had been done. However, this is hard to interpret as a truly stronger association, as it might be due to effects by random since the observations were few and not all cohorts could be included in the meta-analysis.

One might speculate that ex-smoking mothers may start smoking again later, after their maternity leave, when returning to work. This has been seen previously [21]. This was not supported in this material since stratification for maternal smoke exposure at the time of outcome assessment left few women in the current smoking group.

Four individual cohorts showed conflicting results with a tendency towards a protective effect of maternal smoking during pregnancy; DARC (Denmark) for wheeze, GINI-plus (Germany) and AMICS-Menorca (Spain) for asthma. DARC (Denmark) and AMICS-Menorca (Spain) are the smallest cohorts rendering low statistical power. GINI-plus (Germany) collected exposure data on pregnancy smoking at a later stage compared to the other cohorts, thus some recall or reporting bias might be present. Removal of these cohorts from the meta-analysis did not substantially change the combined adjusted OR.

A large Finnish birth cohort study showed that the risk of having asthma at age 7 years increased in a dose-dependent manner, where the information on maternal pregnancy smoking was categorical: non-smoking, < 10 cigarettes/day and > 10 cigarettes/day [18]. A positive dose-dependent effect was confirmed in our study. However, we used a different analysis method with a flexible logistic model estimating the change in OR for every 5 cigarette increase in daily consumption. This method was chosen since most women did not smoke heavily, rendering small numbers in higher consumption

categories. For practical reasons, we used smoking data from the 1st trimester only. Smoking after birth was taken in into account by excluding the children exposed to maternal tobacco smoke in the first year after birth.

There were several strengths with this study. The data was harmonized before meta-analyses, reducing between-study heterogeneity. Recruitment was done during pregnancy or in the first months of life, providing accurate exposure data without substantial recall bias. Response bias was kept to a minimum since exposure data was collected before disease onset. All children were followed prospectively, enabling assessments of possible causal relationships. Furthermore, the statistical power achieved in the combined estimates was to our advantage.

This study was based on parental questionnaire answers both regarding exposure and outcome. Validation with indoor air nicotine or urinary cotinine measurements across several studies has demonstrated that questionnaires used in epidemiological studies for smoke exposure measurement provide sufficiently accurate information for the assessment of impact of parental smoke exposure on respiratory disease in children [25, 26].
Underreporting of parental smoking habits would result in misclassification of smokers as non-smokers. This would probably lead to an underestimation of the observed association. In this study, fewer children exposed to tobacco smoke during pregnancy were included in the analysis compared to the original cohorts which also leads to underestimation of association.

Underutilization of health care has been seen for children with mild respiratory symptoms with mothers who smoke [27]. This might result in under diagnosing of wheeze and asthma in these children. Furthermore, parents of asthmatic children might underreport smoking to a higher extent than those to non-asthmatics [28]. This would result in an underestimation of the association. However, a more recent study did not report this kind of underreporting [25]. In this study, focusing mainly on the effects of smoke exposure during pregnancy, exposure data was collected before disease onset minimizing the risk of recall and response bias due to asthmatic symptoms in the child. Children with allergic disease might be more prone to stay in studies focusing on asthma development although this was not seen in this study.

There were some limitations. The inclusion criteria varied somewhat across the cohorts, some including children only born at term. However, restricting on gestational age for all cohorts did not substantially change the combined ORs. Internal missing observations were unevenly distributed in the individual cohorts, inclusion proportions in the study base ranging from 58 to 96 %. In the meta-analyses, the overall proportion included in the analyses was about 70 %. Confounder sensitivity analysis revealed that some of the changes in the adjusted OR might be due to missing confounder data and not a true confounder effect. However, the results from the combined crude and adjusted estimates did not differ substantially.

All included cohorts had fair data on maternal smoke exposure during pregnancy: one cohort did not report smoke exposure for the different trimesters, only for the whole pregnancy. Another cohort did not have information on number of cigarettes smoked during the 1st trimester and was not included in the dose-response analysis for this reason. The variables for numbers of cigarettes smoked during pregnancy varied in the coding regarding non-smokers. Some cohorts had non-smokers coded as non-cases, and some had them coded as missing observations. Thus, the variable had to be re-coded for the dose-response analysis for two cohorts.
For maternal smoke exposure after delivery, most cohorts asked about smoke exposure in the dwelling but two cohorts did not restrict the smoke exposure to the home.

One cohort had more than 80 % missing observations on wheeze and had to be excluded entirely. One cohort lacked information on asthma diagnosis in the right time frame and was included in the analyses only for the outcome wheeze, not asthma. Information on asthma medication was available from most cohorts although the questions were heterogeneous. In three cohorts, the use of asthma medication reflected the use for the past two years, and in one cohort the use of medication was asked “since last follow up” which was three years earlier (DARC, Denmark). Some cohorts had information on which asthma medication had been used, some only asked for medication yes or no. The asthma diagnosis criteria posed some difficulties. Some cohorts asked for ever having received a diagnosis, some only asked for a diagnosis during the last 12 months. For the latter cohorts, new variables had to be created where the annual questionnaire answers were combined to form a ‘diagnosis ever’-variable. Some observations were lost because of internal missing for these cohorts.

General Conclusion and Recommendation

The ENRIECO collaboration gives access to individual participant data from 47 European cohorts, increasing statistical power enormously. The comparison and quality of the results and combined data analyses would be further improved if standardization of outcome and exposure assessments was done across the cohorts. A general recommendation for which time frames to use (“ever”, “since last follow-up” or “in the last 12 months”) regarding questions on respiratory symptoms, asthma diagnosis and medication would be of great value.

To policy makers

This study proved an independent effect of maternal smoke exposure during pregnancy on the development of wheeze and asthma in children. The tobacco smoking prevalence among pregnant women today is about 20 % [29, 30], and many of these women continue smoking throughout pregnancy [31]. Policy makers should be aware of the important role of tobacco smoke prevention, especially among young girls, fertile women, and their partners during the childbearing years.

References

1. Pattenden, S., et al., *Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure.* Tob Control, 2006. **15**(4): p. 294-301.
2. Wang, L. and K.E. Pinkerton, *Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma.* Birth Defects Res C Embryo Today, 2008. **84**(1): p. 54-60.
3. Stocks, J. and C. Dezateux, *The effect of parental smoking on lung function and development during infancy.* Respirology, 2003. **8**(3): p. 266-85.
4. Kumar, R., *Prenatal factors and the development of asthma.* Curr Opin Pediatr, 2008. **20**(6): p. 682-7.
5. Oberg, M., et al., *Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries.* Lancet, 2011. **377**(9760): p. 139-46.
6. Landrigan, P.J. and J.E. Carlson, *Environmental policy and children's health.* Future Child, 1995. **5**(2): p. 34-52.
7. Moya, J., C.F. Bearer, and R.A. Etzel, *Children's behavior and physiology and how it affects exposure to environmental contaminants.* Pediatrics, 2004. **113**(4 Suppl): p. 996-1006.
8. Foundas, M., et al., *Urinary cotinine levels in early pregnancy.* Aust N Z J Obstet Gynaecol, 1997. **37**(4): p. 383-6.
9. Lackmann, G.M., et al., *Metabolites of a tobacco-specific carcinogen in urine from newborns.* Journal of the National Cancer Institute, 1999. **91**(5): p. 459-465.
10. Wu, F.Y., et al., *Comparison of urinary and plasma cotinine levels during the three trimesters of pregnancy.* Paediatr Perinat Epidemiol, 2008. **22**(3): p. 296-301.
11. Hofhuis, W., J.C. de Jongste, and P.J. Merkus, *Adverse health effects of prenatal and postnatal tobacco smoke exposure on children.* Archives of Disease in Childhood, 2003. **88**(12): p. 1086-90.
12. Wu, Z.X., et al., *Prenatal and early, but not late, postnatal exposure of mice to sidestream tobacco smoke increases airway hyperresponsiveness later in life.* Environ Health Perspect, 2009. **117**(9): p. 1434-40.
13. Kurukulaaratchy, R.J., et al., *Characterization of wheezing phenotypes in the first 10 years of life.* Clin Exp Allergy, 2003. **33**(5): p. 573-8.
14. Goksor, E., et al., *The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness.* Acta Paediatr, 2007. **96**(7): p. 1030-5.
15. Gilliland, F.D., Y.F. Li, and J.M. Peters, *Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children.* Am J Respir Crit Care Med, 2001. **163**(2): p. 429-36.
16. Lannero, E., et al., *Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE).* Respir Res, 2006. **7**: p. 3.
17. Gilliland, F.D., et al., *Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function.* Am J Respir Crit Care Med, 2003. **167**(6): p. 917-24.
18. Jaakkola, J.J. and M. Gissler, *Maternal smoking in pregnancy, fetal development, and childhood asthma.* Am J Public Health, 2004. **94**(1): p. 136-40.
19. Magnusson, L.L., et al., *Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life.* Clin Exp Allergy, 2005. **35**(12): p. 1550-6.
20. Alati, R., et al., *In utero and postnatal maternal smoking and asthma in adolescence.* Epidemiology, 2006. **17**(2): p. 138-44.
21. Murin, S., R. Rafii, and K. Bilello, *Smoking and smoking cessation in pregnancy.* Clin Chest Med, 2011. **32**(1): p. 75-91.
22. Torrent, M., et al., *Smoking cessation and associated factors during pregnancy.* Gac Sanit, 2004. **18**(3): p. 184-9.
23. Asher, M.I., et al., *International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods.* Eur Respir J, 1995. **8**(3): p. 483-91.
24. Hoo, A.F., et al., *Respiratory function among preterm infants whose mothers smoked during pregnancy.* Am J Respir Crit Care Med, 1998. **158**(3): p. 700-5.
25. Gehring, U., et al., *Comparison of parental reports of smoking and residential air nicotine concentrations in children.* Occup Environ Med, 2006. **63**(11): p. 766-72.
26. Brunekreef, B., et al., *Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy.* Epidemiology, 2000. **11**(3): p. 350-2.

27. Jacobs-van der Bruggen, M.A., et al., *Do parents who smoke underutilize health care services for their children? A cross sectional study within the longitudinal PIAMA study.* BMC Health Serv Res, 2007. **7**: p. 83.
28. Clark, S.J., J.O. Warner, and T.P. Dean, *Passive smoking amongst asthmatic children. Questionnaire or objective assessment?* Clin Exp Allergy, 1994. **24**(3): p. 276-80.
29. Jaddoe, V.W., et al., *Maternal smoking and fetal growth characteristics in different periods of pregnancy: the generation R study.* Am J Epidemiol, 2007. **165**(10): p. 1207-15.
30. Goodwin, R.D., K. Keyes, and N. Simuro, *Mental disorders and nicotine dependence among pregnant women in the united states.* Obstetrics and Gynecology, 2007. **109**(4): p. 875-883.
31. Goedhart, G., et al., *Psychosocial problems and continued smoking during pregnancy.* Addict Behav, 2009. **34**(4): p. 403-6.

Appendix

Table 1. Characteristics of the eight European birth cohorts including prevalence of maternal smoking prevalence during pregnancy, in the first year after delivery and at the time of outcome assessments as well as prevalence of wheeze and asthma age 4 to 6 years.

Birth cohort	Country	Enrolment period	Number of recruited children	Child's age at recruitment	Mean birth weight (grams)[1]	Mother smoked during pregnancy n (%)[2]	Mother smoked 1st year after delivery n (%)[3]	Mother smoked at age 4-6 years n (%)[4]	Wheeze at age 4-6 years n (%)[5]	Asthma at age 4-6 years n (%)[6]
ALSPAC	UK	1991-1992	14,057	During pregnancy	3384	3670 (27.5)	3606 (33.9)	1918 (24.8)	829 (9.9)	-
AMICS-Menorca	Spain	1997-1998	482	During pregnancy	3187	182 (37.9)	152 (32.8)	112 (24.3)	41 (8.9)	34 (7.4)
BAMSE	Sweden	1994-1996	4089	Shortly after birth[5]	3530	529 (12.9)	584 (14.8)	534 (14.3)	546 (14.7)	512 (13.7)
DARC	Denmark	1998-1999	562	Shortly after birth[5]	3541	183 (32.6)	154 (29.8)	88 (19.1)	27 (5.9)	18 (4.1)
GINI-plus	Germany	1995-1998	5991	Shortly before or after birth	3472	723 (15.1)	--[7]	428 (12.4)	341 (8.9)	135 (3.5)
LISA	Germany	1997-1999	3097	Shortly after birth[5]	3473	536 (18.0)	362 (16.4)	177 (8.8)	208 (9.5)	70 (3.2)
MAS	Germany	1990	1314	Shortly after birth[5]	3409	308 (25.4)	443 (38.9)	272 (27.6)	103 (10.5)	34 (3.8)
PIAMA-NHS	The Netherlands	1996-1997	3182	During pregnancy	3515	839 (26.5)	546 (17.6)	419 (14.5)	278 (9.7)	122 (4.4)

[1] GINI, LISA and DARC recruited children born at term, i.e. from pregnancy week 37.
[2] Mother smoked at least one cigarette daily during any time of pregnancy.
[3] Mother smoked during the first year after delivery.
[4] Mother smoked at the time of outcome assessment, i.e. when the child was 4, 5 or 6 years of age.
[5] Outcome data from follow-ups when the children were 5 years of age except for BAMSE (age 4 y) and ALSPAC (age 6 y).
[6] First questionnaire at age 1 month in MAS and DARC, age 2 months in BAMSE, median age 3 days in LISA.
[7] Insufficient information on maternal smoking during the first year of life.

Table 2. Prevalence of maternal smoking during pregnancy and during the first year after delivery in eight European birth cohorts comprising 22,628 children included in the meta-analyses. Maternal smoking is allocated into four disjunctive categories.

Birth cohort	No smoking (reference) n (%)[1]	Smoking during pregnancy only n (%)[2]	Smoking in the first year only n (%)[3]	Smoking during pregnancy and 1st year n (%)[4]
ALSPAC	5460 (71.2)	157 (2.1)	407 (5.3)	1584 (20.8)
AMICS-Menorca	268 (60.8)	28 (6.3)	12 (2.7)	133 (30.2)
BAMSE	3051 (83.1)	93 (2.5)	153 (4.2)	376 (10.2)
DARC	315 (63.6)	35 (7.1)	17 (3.4)	128 (25.9)
GINI-plus	--[5]	--[5]	--[5]	--[5]
LISA	1421 (80.7)	106 (6.0)	67 (3.8)	166 (9.4)
MAS	561 (63.6)	18 (2.0)	127 (13.9)	188 (20.6)
PIAMA-NHS	2168 (74.2)	287 (9.8)	18 (0.6)	448 (15.3)
TOTAL	13,244(74.4)	724 (4.1)	801 (4.5)	3023 (17.0)

[1] No maternal smoking during pregnancy or in the first year after delivery.
[2] Maternal smoking of at least one cigarette daily during any time of pregnancy, but no smoking during the first year after delivery.
[3] No maternal smoking during pregnancy, but maternal smoking during the first year after delivery.
[4] Maternal smoking of at least one cigarette daily during any time of pregnancy and during the first year after delivery.
[5] No information on maternal smoking during the first year of life.

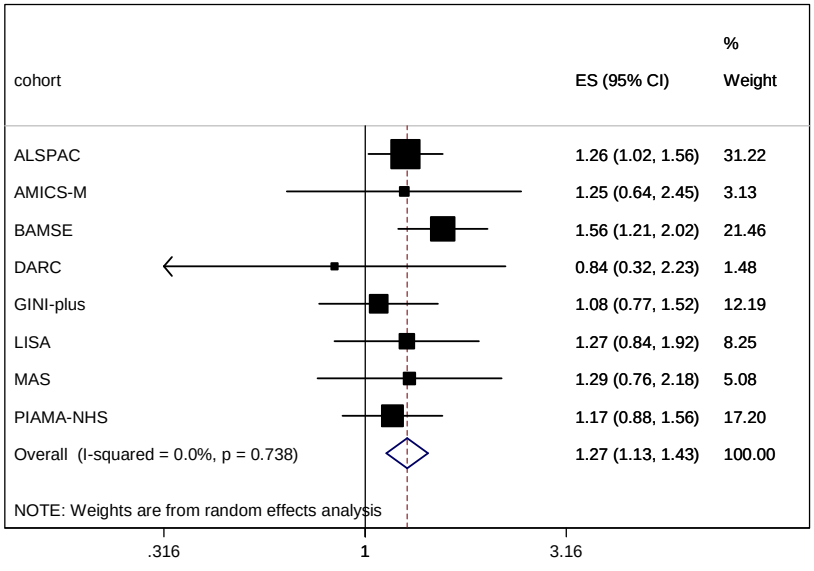
Table 3. Associations between maternal smoking during pregnancy and wheeze or asthma at age 4-6 years in 8 European birth cohorts. Crude odds ratios (OR) and 95% confidence intervals (95% CI) for the individual studies obtained by logistic regression.

	Maternal smoking during pregnancy			Maternal smoking during pregnancy, but not in the child's first year of life		
	n/ Total N	Crude OR	95 % CI	n/ Total N	Crude OR	95 % CI
WHEEZE						
ALSPAC	207/8116	1.31	1.11-1.55	17/7608	1.20	0.72-2.00
AMICS-M	18/457	1.33	0.70-2.55	3/441	1.34	0.37-4.80
BAMSE	104/3709	1.80	1.42-2.29	25/3653	2.33	1.46-3.73
DARC	7/461	0.75	0.31-1.82	1/421	0.50	0.06-3.87
GINI-plus	53/3756	1.24	0.91-1.69	-[1]	-[1]	-[1]
LISA	37/1968	1.35	0.92-1.98	17/1746	1.78	1.03-3.08
MAS	25/916	1.24	0.76-2.01	2/888	1.06	0.24-4.71
PIAMA-NHS	78/2861	1.19	0.90-1.57	27/2841	1.04	0.68-1.59
ASTHMA						
ALSPAC	-[2]	-[2]	-[2]	-[2]	-[2]	-[2]
AMICS-M	16/456	1.52	0.75-3.06	2/440	1.06	0.23-4.84
BAMSE	98/3729	1.80	1.41-2.30	24/3673	2.28	1.42-3.67
DARC	7/441	1.61	0.61-4.24	2/429	1.79	0.38-8.46
GINI-plus	17/3747	0.98	0.58-1.64	-[1]	-[1]	-[1]
LISA	17/1964	2.06	1.17-3.62	7/1743	2.40	1.05-5.49
MAS	13/837	2.39	1.16-4.90	2/814	4.18	0.88-19.88
PIAMA-NHS	34/2729	1.18	0.79-1.77	10/2711	0.90	0.46-1.75

[1] No information on maternal smoking during the first year of life.
[2] No asthma outcome available.

Figure 1. Associations between maternal smoking during pregnancy *irrespective of smoke exposure in the 1st year after delivery* in relation to wheeze and asthma age 4 to 6 years in 8 European birth cohorts. Individual odds ratios (OR) and 95 % confidence intervals (95% CI) for each individual study obtained by logistic regression and combined OR and 95% CI derived by random effects methods. For each study, the size of the square represents the variance of the individual cohort. Adjustments were made for sex, parental asthma, parental education, older siblings and birth weight.

A. Wheeze age 4 to 6 years



B. Asthma age 4 to 6 years

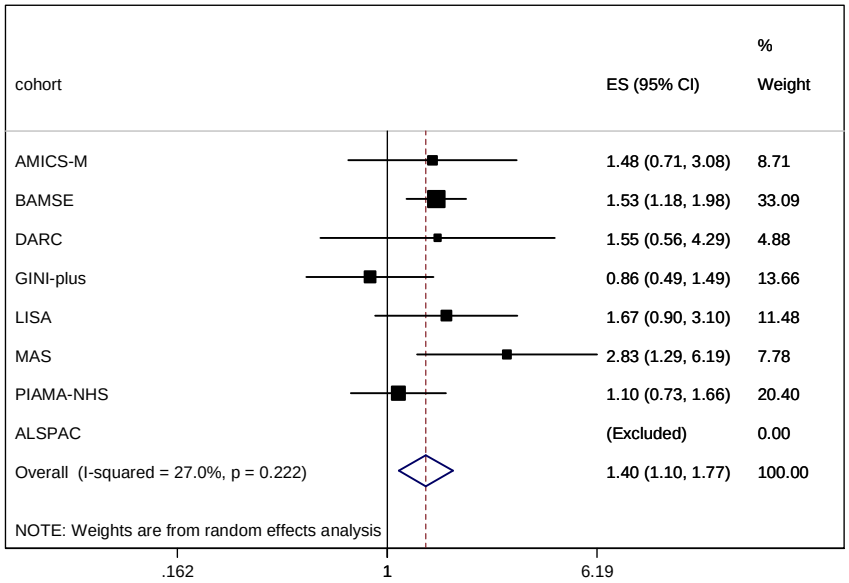
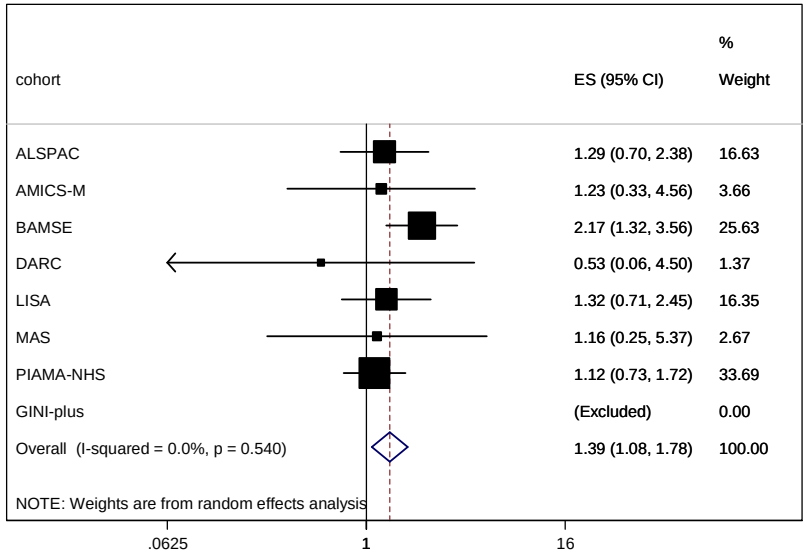
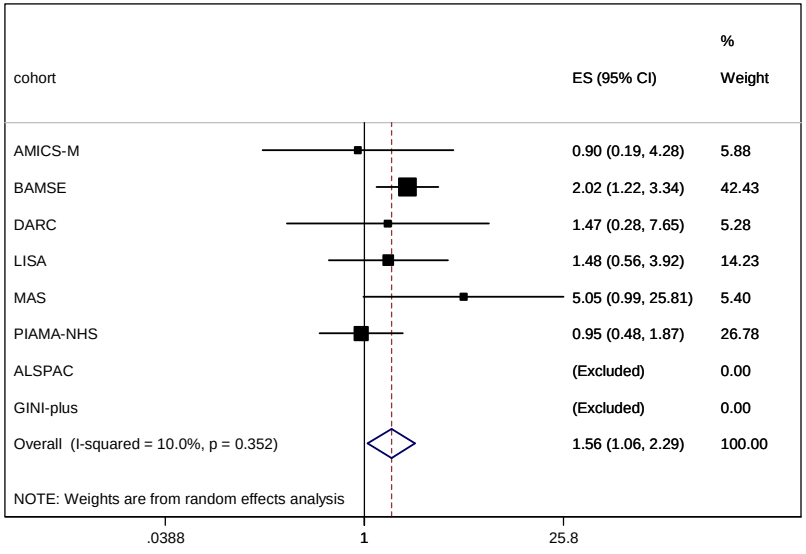


Figure 2. Associations between maternal smoking during pregnancy, *but no maternal smoke exposure during the child's first year of life*, in relation to wheeze and asthma age 4 to 6 years in 8 European birth cohorts. Individual odds ratios (OR) and 95 % confidence intervals (95% CI) for each individual study obtained by logistic regression and combined OR and 95% CI derived by random effects methods. For each study, the size of the square represents the variance of the individual cohort. Adjustments were made for sex, parental asthma, parental education, older siblings and birth weight.

A. Wheeze age 4 to 6 years



B. Asthma age 4 to 6 years



Working Group 3: Second Hand Smoke Exposure and Wheezing from Birth to Two Years of Age

Researchers involved: Constantine Vardavas, Evridiki Patelarou, Vassilaki M, Mark Nieuwenhuijsen and Manolis Kogevinas

Background

Exposure to secondhand smoke (SHS) is a serious public health hazard. It has been estimated that at least 1000 million adults are smokers worldwide and that at least 700 million children breathe air polluted by tobacco smoke at home [1, 2]. SHS itself comprises sidestream smoke emitted from the smouldering tobacco between puffs and exhaled mainstream smoke from the smoker. Both sidestream and mainstream smoke affect not only tobacco users but also passively other people who share their close environment [2]. Indeed, passive smoking in children diminishes pulmonary function, increases the risk of lower respiratory tract illness, exacerbates asthma and possibly even leads to an increased risk for the development of asthma [3]. Existing reviews have also stressed that prenatal maternal smoking has been shown to increase the risk for the development of symptomatic pediatric asthma while postnatal maternal smoking is associated with an increased incidence of wheezing illness up to the age of 6. [4-5]

A number of maternal and lifestyle factors have been shown to be associated with the occurrence of wheezing or diagnosed asthma in childhood and adolescence, such as maternal age [6-8], maternal smoking before birth and exposure to SHS [9-12]. Maternal smoking, low maternal age and early bottle feeding are also associated with lower respiratory tract illness in the first 2 years of life as also environmental exposures such as dampness [9, 13-15], which, in turn, is linked with the development of asthma in childhood [16-18]. Moreover, research has indicated that fetal breathing movements are essential for normal growth and structural maturation of fetal lungs and within such studies nicotine has been shown to cause a reduction in the incidence of fetal breathing movements in normal and abnormal human pregnancies. [19-20]. Collectively this evidence therefore suggests that exposures occurring during pregnancy and early childhood can influence the risk of respiratory signs, such as wheezing in early childhood, or asthma later on in life.

While the above causal relationships are of significant importance to both pediatrics and public health, the international literature contains a remarkable lack of information on the development of respiratory symptoms among infants exposed in utero or post utero to SHS, while controlling for possible confounding factors. With this in mind, we aimed to assess the role of prenatal and postnatal exposure to SHS (together and independently) on the development of wheezing up to 2 years of age. Secondly we aimed to investigate into the possible coherent interaction between active smoking and passive smoking on the development of wheezing before age 2.

Methods

Inclusion criteria

Inclusion criteria were: (i) European population-based observational birth cohort studies; (ii) recruitment of newborns in pregnancy; (iii) ≥1 follow-up assessment until at least 2 years of age; (iv) maternal active smoking and SHS exposure classified at least once during pregnancy and once during infancy; (v) information on the development of wheezing available sometime during infancy before the age of 2. A list of the included European birth cohorts that fulfil the inclusion criteria can be found in the table below.

Table 1. Participating cohorts in the case study of WG 3 on second hand smoke exposure and wheezing at age 0-2 years.

No	Cohort name	Country of origin
1	ALSPAC	UK
2	AMICS	UK-Spain
3	BAMSE	Sweden
4	CO.N.ER	Italy
5	DARC	Denmark
6	Generation R	The Netherlands
7	GINI	Germany
8	INMA Asturias	Spain
9	INMA Guipuzkoa	Spain
10	INMA Sabadell	Spain
11	INMA Valencia	Spain
12	KOALA	The Netherlands
13	Leicester	UK
14	LISA	Germany
15	MAS	Germany
16	NINFEA	Italy
17	PIAMA-NHS	The Netherlands
18	PELAGIE	France
19	RHEA	Greece

Definition of the primary outcome

Wheezing was assessed as the primary outcome (yes/no). Wheezing was either based on the ISAAC core question if available or on parental self report. Where possible physician diagnosed wheezing was also taken into account. The reported age for developing wheezing up to the age of 2 differed within the cohorts and thus that factor was taken into account investigating into the appearance of wheezing (i) up to 6 months, (ii) up to 12 months and, (iii) up to 24 months of age.

Ethics approval

This research was conducted according to the principles expressed in the Declaration of Helsinki. The included birth cohort studies were all approved by their local Institutional Review Boards. All participants provided written informed consent for data collection and analysis.

Definitions of exposure factors

Active and passive smoking during pregnancy were taken into account in the analysis as also the combined effect of passive smoking during infancy with both active and passive smoking during pregnancy. Following this categorization, a number of distinct exposure groups were created based on the different combinations of exposure. The main subgroups of exposure are:

(i) Non exposed to SHS during pregnancy and non exposed to SHS during infancy.
(ii) Exposed to SHS during pregnancy and SHS during infancy.
(iii) Exposed to SHS during pregnancy but unexposed to SHS during infancy.
(iv) Unexposed to SHS during pregnancy and exposed to SHS during infancy.
(v) Exposed to active smoking (maternal) during pregnancy and SHS (maternal) during infancy.
(vi) Exposed to active smoking (maternal) and passive smoking (paternal) during pregnancy and SHS (maternal+paternal) during infancy.

According on the sample size and the analysis (separate or pooled) different categories will be further assessed. Former smoking will also be assessed in the pooled analysis.

Confounding factors

Confounding factors that are known to influence the development of wheezing during childhood will be taken into account in the multivariate analysis. These can be grouped in 3 categories (pregnancy and family history; environmental factors; sociodemographic factors).
Pregnancy related: birthweight, gestational age, mode of delivery, gender, family history of asthma.
Sociodemographic: Educational level of mother, educational level of father
Environmental: dampness in the house (yes/no), pets (yes/no), breastfeeding (in months), day care attendance (yes/no), bedroom sharing (yes/no).

Statistical analysis

Initially variables will be checked for computational mistakes, descriptive statistical procedures will be performed, followed my bivariate analyses with the use of student t-tests, the chi squared test and ANOVA. Following the bivariate analysis multiple logistic regression analyses will be performed taking confounding factors into account. All test will be two sided and a $p<0,05$ will be regarded as statistically significant. The statistical packages SPSS 18.0 and STATA 10.0 will be used to perform the analyses. Furthermore, the analyses will also be stratified by each exposure category so as to assess the role of each combination of exposure separately. Based on the adequacy of the information on confounding factors each cohort will be assessed separately, or together so as to either perform a meta-analysis or a pooled regression.

Results

WG 3 was initially not part of the ENRIECO project and is an additional case study which was originated at the first ENRIECO meeting in May 2009. Final results are still to come.

Discussion

WG 3 was initially not part of the ENRIECO project and is an additional case study which was originated at the first ENRIECO meeting in May 2009. Final results are still to come.

References

World Health Organization Division of Noncommunicable Disease, Tobacco Free Initiative. International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. Consultation Report, Geneva 1999. http://www.who.int/tobacco/research/en/ets_report (viewed 04 / 07 / 05)

US Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: A report of the Surgeon General. Atlanta, G.A: US Department of Health and Human services, Center for Disease Control and Prevention, Coordinating Center of Health promotion, National Center for Chronic Disease Prevention and Health Promotion. Office on Smoking and Health, 2006. Available at http://www.surgeongeneral.gov/library/secondhandsmoke/report/index.html

Chan-Yeung M, Dimich-Ward H, 2003. Respiratory health effects of exposure to environmental tobacco smoke. Respirology. 8, 131–139

von Mutius E. Environmental factors influencing the development and progression of pediatric asthma. J Allergy Clin Immunol 2002;109 (suppl) S525–32.

Strachan DP, Cook DG. Health effects of passive smoking. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 1998;53:204–12.

Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Am Rev Respir Dis 1990; 142: 555–562.

Anderson HR, Bland JM, Peckham CS. Risk factors for asthma up to 16 years of age. Chest 1987; 91: 127s–130s.

Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. J Epidemiol Commun Health 1986; 40: 121–129.

Martinez FD, Wright AL, Holberg CJ, Morgan WJ, Taussig LM. Maternal age as a risk factor for wheezing lower respiratory illnesses in the first year of life. Am J Epidemiol 1992; 136: 1258–1268

Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. Pediatr 1990; 85:505–511.

Somerville SM, Rona RJ, Chinn S. Passive smoking and respiratory conditions in primary school children. J Epidemiol Commun Health 1988; 42: 105–110.

Pattenden S, Antova T, Neuberger M, Nikiforov B, De Sario M, Grize L, Heinrich J, Hruba F, Janssen N, Luttmann-Gibson H, Privalova L, Rudnai P, Splichalova A, Zlotkowska R, Fletcher T. Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. Tob Control. 2006; 15(4):294-301.

Fergusson DM, Horwood LJ, Shannon FT. Parental smoking and respiratory illness in infancy. Arch Dis Child 1980; 55: 358–361.

Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. Arch Dis Child 1987; 62: 786–791.

Pirastu R, Bellu C, Greco P, Pelosi U, Pistelli R, Accetta G, Biggeri A. Indoor exposure to environmental tobacco smoke and dampness: respiratory symptoms in Sardinian children--DRIAS study. Environ Res. 2009; 109(1):59-65.

Weiss ST, Tager IB, Munoz A, Speizer FE. Relationship of respiratory infections in early childhood to occurrence of increased levels of bronchial responsiveness and atopy Am Rev Respir Dis 1985; 131: 573–578.

Pullan CR, Hey EN. Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. Br Med J 1982; 284: 1665–1669.

Wang L, Pinkerton KE. Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma. Birth Defects Res C Embryo Today. 2008;84(1):54-60

Harding R. Fetal pulmonary development: the role of respiratory movements. Equine Vet J Suppl 1997;(24):32–9.

Manning FA, Feyerabend C. Cigarette smoking and fetal breathing movements. Br J Obstet Gynaecol 1976;83:262–70.