



HEALS

Health and Environment-wide Associations
based on Large population Surveys

FP7-ENV-2013- 603946

<http://www.heals-eu.eu/>

D14.2 Report on the refined HEALS methodology for estimating the health effects of exposure to multi-pollutant mixtures and allergens in the air

**WP 14. Allergy and asthma -
link with particulate matter (PM) and biological**

Lead beneficiary: CNR

AIM:

The overall aim of WP14 is to develop approaches, methods and scientific knowledge for converting information on combined exposures to particulate matter (PM) and allergens into quantitative estimates of their effects on allergy and asthma.

The first step to reach this aim was presented in D14.1 and it consisted in the collection of pre-existing European datasets on asthma and allergies and risk factors.

The second step, described in this D14.2, consists in the implementation of a scientific report on the results of the statistical analyses performed on the HEALS database to investigate the links between asthma and allergy and exposure to air pollutants and allergens.

MATERIALS AND METHODS:

Study population

Pre-existing European cohorts with information about asthma and allergies and air pollution and allergens exposures were selected: 6 studies on children samples and 5 studies on general population samples, for a total of about 27000 subjects.

The HEALS database consists of the following studies (table 1):

a) Children samples: 1) the CCM study, an Italian cross-sectional study on 2573 children, 6-15 years of age, investigated in the period 2010-2012; 2) the REPRO_PL study, a Polish longitudinal cohort of 539 children, 0-7 years of age, investigated in the period 2006-2015 at 1, 2 and 7 yrs of age; 3) the MAAS study, a UK longitudinal cohort of 1184 children, 1-17 years of age, investigated in the periods 1997-2000 (1 yr of age), 1999-2002 (3 yrs), 2001-2004 (5 yrs), 2004-2007 (8 yrs), 2007-2010 (11 yrs) and 2011-2014 (about 17 yrs); 4) the EPITEEN study, a Portuguese cross-sectional study on 2942 children, 13 years of age, investigated in the period 2003-2004; 5) the G21 study, a Portuguese longitudinal cohort of 8647 children, 0-7 years of age, investigated in the periods 2005-2006 (at birth), 2009-2012 (at 4 yrs of age), 2012-2014 (at 7 yrs); 6) the EDEN study, a French longitudinal cohort of 2002 children, 0-7 years of age, investigated in the period 2003-2012 at birth, at 1, 2, 3, 4, 5 and 7 yrs of age.

b) General population samples: 1) the PISA1 study, an Italian cross-sectional study on 3865 subjects, 4-97 years of age, investigated in the period 1985-1988; 2) the PISA2 study, an Italian cross-sectional study on 2841 subjects, 8-97 years of age, investigated in the period 1991-1993; 3) the IMCA study, an Italian cross-sectional study on 1620 subjects, 18-103 years of age, investigated in the period 2009-2011; 4) the SEASD study, an Italian cross-sectional study on 639 females, 13-99 years of age, investigated in the period 1997-1998; about 50% of the Italian subjects participated at least in two of the above mentioned studies; 5) the CHIS2000 study, a Spanish cross-sectional study on 919 subjects, 18-74 years of age, investigated in the period 2001-2002.

Outcomes and environmental exposure

General characteristics and confounders (by questionnaire): sex, age, body mass index (BMI), asthma/allergic disease familiarity (a proxy of heritable genetic factors), childhood respiratory infections, smoking habits (in general population samples).

Disease outcomes (by questionnaire): lifetime asthma diagnosis, asthma severity, wheeze, dry cough, eczema, allergic rhinitis (AR) diagnosis, AR severity, AR symptoms.

Asthma and allergic disease biomarkers (by instrumental measurements): airway obstruction (AO) computed according to the GOLD criterion ($FEV_1/FVC < 70\%$), positivity to skin prick test (SPT), blood eosinophilia (blood eosinophils level $> 450/\mu l$), presence of dust/animals specific serum IgE, bronchial hyper-responsiveness (BHR).

Sources of exposure to allergens and air pollutants (by questionnaire): *for allergens*: mould exposure at home, pets exposure at home, cockroaches exposure at home, presence of carpets at home; *for air pollutants exposure*: passive smoke exposure (proxy of indoor PM exposure), air pollution exposure near home and near school, vehicular traffic near home, home distance from main roads ≤ 100 meters and work-related exposure to gases/fumes/dusts (in general population samples).

Outdoor air pollutants concentration at city level (by instrumental measurements): data about outdoor air pollutants concentration at city level were extracted from the HEALS EDMS website (<http://heals.uowm.gr/eea>). This is a website implemented within the HEALS project that contains data extracted from the European Environment Agency database about air pollution measured through monitoring stations. In particular, data about the concentration of nitrogen dioxide (NO₂), particulate matter (PM₁₀ and PM_{2.5}) and ozone (O₃) of the cities involved in the HEALS pre-existing studies were extracted. For some studies, PM_{2.5} data were missing due to the fact that PM_{2.5} were not routinely monitored in the study periods.

In particular, for each city, the following values were computed: a) mean annual concentration during the study period; b) concentration values above the EU reference values and above the WHO Air Quality guidelines values; c) concentration values above the 75th percentile of the distribution of the air pollutants concentration of the involved cities.

Indoor/outdoor PM concentration at school/home (by instrumental measurements): in EDEN and CCM studies, short term campaigns to measure the PM concentration at school and, only in EDEN, at home were performed. In particular, PM_{2.5} concentrations inside the classroom and outside school, PM₁₀ concentration inside the classroom and PM_{2.5} concentrations outside home were measured.

Allergens concentration inside the classroom (by instrumental measurements): in CCM study, concentrations of cat, dog and mites allergens in dust, collected by vacuum inside the classrooms, were measured. Children attending a classroom with a concentration of allergens higher than the value of the 75th percentile of the distribution of each allergen concentrations were considered as exposed.

Harmonized HEALS database

An intensive work was done to harmonize the pre-existing European datasets in a unique database containing all the information about health outcomes, biomarkers, allergens and air pollution exposure coming from different studies and collected through the use of questionnaires and, in some subsamples, by instrumental measurements.

After this time consuming phase, a depth control on data quality was performed.

Table A shows the available data in each of the individual study of the HEALS database. Overall an adequate comparability among the studies for the health outcomes variables was found; a higher difficulty emerged for the exposure variables. Only 3 pairs of studies had common exposure variables collected by questionnaires: CCM and REPRO_PL studies, CCM and EDEN studies for children samples, PISA2 and IMCA studies for general population samples.

Statistical analyses

Different statistical analyses were performed on different subsamples to address the WP14 aims: to assess the relationships between joint exposure to air pollutants and aero-allergens and the prevalence and severity of allergy and asthma at the population level in Europe; to investigate the joint impact of air pollutants and aero-allergens exposure on asthma and allergies using objective measurements of the health effects like health biomarkers.

Based on the common exposure variables (see table A), the following samples were analyzed:

Step 1, children and general population individual study (i.e. CCM, MAAS, EDEN studies..);

Step 2, children and general population HEALS subsamples having common exposure variables collected from questionnaires;

Step 3, HEALS entire children sample (with exception of MAAS and EPITEEN studies) having common exposure variables collected from questionnaires (table A) and from the HEALS EDMS website.

The following statistical analyses were performed:

a) Assessment of independent effect of exposure to air pollutants and allergens

Bivariate (chi-square test) and multivariable statistical analyses to assess the independent effects of air pollution and allergens exposure on health status were run.

In particular, multivariable logistic regression analyses, including the disease outcomes and biomarkers as dependent variables and anthropometric parameters (age, sex, BMI), asthma/allergic disease familiarity, childhood respiratory infections and allergens/environmental exposure as independent variables were performed.

With regards to the air pollution exposure assessment, data coming from air pollution monitoring stations were not used in the individual studies analyses (Step 1) due to the steadiness of the pollution concentration mean value in the study period within the single study/city. Only data from questionnaires were used.

On the contrary, in Step 2 and Step 3, it was possible to take into account air pollution data extracted from the monitoring stations (EDMS database), too. Each air pollutants concentration was categorized as below/above 75th percentile; the choice of using this cut-off was due to the fact that the cities involved in the HEALS study were generally characterized by low levels of air pollution concentration (almost all of these below the EU reference values for PM). Two different approaches were used: a) independent effect of being exposed to at least one concentration value above the 75th percentile; b) independent effect of different clusters of air pollutants exposure (“air pollutants cluster”).

As regards the “air pollutants cluster”, it was identified through a Latent Class Analysis (LCA): cluster 1, subjects exposed to only $O_3 \geq 75$ th percentile; cluster 2, subjects exposed to only $NO_2 \geq 75$ th percentile; cluster 3, subjects exposed to only PM_{10} & $PM_{2.5} \geq 75$ th percentile.

b) Effect of combined exposure to air pollutants and allergens:

To assess the effect of combined exposure to air pollutants and allergens, 4 different statistical approaches were used:

First approach: multivariable logistic regression analyses with interaction terms to compare the effect of only allergens or only air pollutants exposure to both allergens and air pollutants exposure.

Second approach: multivariable logistic regression analyses carried out after stratifying the sample by the concentration values of air pollutants below and above the 75th percentile to assess the effect of allergens exposure in subjects exposed to low or high concentration of air pollutants.

Third approach: multivariable logistic regression analyses carried out after stratifying the sample by the “air pollutants cluster” to assess the effect of allergens exposure in subjects exposed to different patterns of air pollutants.

Fourth approach: multivariable logistic regression analysis carried out taking as dependent variables the disease outcomes, and as independent variables anthropometric parameters (age, sex) and the “combined exposure cluster” to assess the effect of the combined exposure to allergens, air pollutants and asthma/allergic familiarity. As regards the “combined exposure cluster”, it was identified through a LCA: cluster 1, children only exposed to allergens; cluster 2, children with asthma/allergic disease familiarity and exposed to allergens and high levels of O_3 concentration (≥ 75 th percentile); cluster 3, children with asthma/allergic disease familiarity and exposed to allergens and high levels of PM_{10} , $PM_{2.5}$, NO_2 (≥ 75 th percentile).

The effect of combined exposure to air pollutants and allergens were only assessed on the HEALS children database; this choice was due to the higher number of available information about health outcomes and exposure in children samples with respect to general population samples.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), rel 16.0. LCA was run using the R statistical package 3.4.2.

A p-value ≤ 0.05 was considered statistically significant, a $0.05 < p\text{-value} < 0.10$ was considered as borderline significance.

RESULTS:

Frequency of investigated outcomes and allergens & pollutants exposure

Tables 2-3 show the prevalence of disease outcomes and disease biomarkers in the HEALS database.

In children sample, the overall prevalence rates of disease outcomes were 12.5% for asthma (of which 28.8% was severe asthma), 43.5% wheeze, 32.6% dry cough, 21.4% eczema, 18.1% AR diagnosis (of which 69.9% was severe AR) and 33.0% AR symptoms (table 2).

In general population sample, the overall prevalence rates of disease outcomes were 7.0% for asthma, of which 7.0% was severe asthma (information available only in PISA2), 20.2% wheeze, 15.7% dry cough, 13.1% eczema, 17.8% AR diagnosis, of which 14.8% was severe AR (information available only in PISA2 study) and 37.5% AR symptoms (information available only in IMCA study) (table 2).

With regards to the disease biomarkers, they were only available in a subsample of the HEALS database (CCM, EDEN, MAAS, REPRO_PL, IMCA, PISA2, SEASD studies) (table 3).

In children sample, the overall prevalence rates of disease biomarkers were 1.5% AO, 35.3% SPT positivity, 16.9% blood eosinophilia (information available only in EDEN study), 13.9% elevated specific IgE and 18.4% BHR (information available only in MAAS study) (table 3).

In general population sample, the overall prevalence rates of disease biomarkers were 14.1% AO, 32.1% SPT positivity (information available only in PISA2), 3.5% blood eosinophilia and 28.0% BHR (information available only in PISA2 study) (table 3).

Tables 4-6 show the prevalence of allergens and environmental pollutants exposure in HEALS database.

As regards the sources of exposure to allergens and air pollutants collected by questionnaire, not all the samples had complete information (table 4) (table A).

In children sample, the prevalence rates of exposure were 55.5% passive smoke exposure, 24.6% mould exposure at home, 19.9% pets exposure at home, 14.3% cockroaches exposure at home, 22.1% presence of carpets at home, 77.7% air pollution sources near home. Only for CCM study sample: 61.6% home distance $\leq 100\text{m}$ from main roads, 89.6% vehicular traffic exposure near home, 77.9% air pollution sources exposure near school (table 4).

In general population sample, the prevalence rates of exposures were 47.1% passive smoke exposure, 47.4% pets exposure at home, 61.8% air pollution sources exposure near home, 48.9% vehicular traffic exposure near home and 40.0 % occupational exposure; only PISA2 study had information about home distance $\leq 100\text{m}$ from main roads (28.4%) (table 4).

In children sample, the overall annual mean concentrations of air pollutants were $39.2 \mu\text{g}/\text{m}^3$ O_3 , $41.4 \mu\text{g}/\text{m}^3$ NO_2 , $33.9 \mu\text{g}/\text{m}^3$ PM_{10} , $16.9 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ (table 5). Considering the EU reference values of air pollutants concentration, 80% of the European children samples were exposed to $\text{NO}_2 \geq 40 \mu\text{g}/\text{m}^3$, no child was exposed to $\text{PM}_{10} \geq 40 \mu\text{g}/\text{m}^3$ and 10.8% were exposed to $\text{PM}_{2.5} \geq 25 \mu\text{g}/\text{m}^3$. Considering the WHO Air Quality guidelines for air pollutants concentration, 80% of the European children samples were exposed to $\text{NO}_2 \geq 40 \mu\text{g}/\text{m}^3$, 100.0% to $\text{PM}_{10} \geq 20 \mu\text{g}/\text{m}^3$ and 78.7% to $\text{PM}_{2.5} \geq 10 \mu\text{g}/\text{m}^3$ (table 5). Considering the 75th percentile of air pollutants concentration, 23.1% of the European children samples were exposed to $\text{O}_3 \geq 75\text{th percentile}$ ($48.7 \mu\text{g}/\text{m}^3$), 28.6% to $\text{NO}_2 \geq 75\text{th percentile}$ ($60.7 \mu\text{g}/\text{m}^3$), 21.4% to $\text{PM}_{10} \geq 75\text{th percentile}$ ($42.3 \mu\text{g}/\text{m}^3$) and 20.0% to $\text{PM}_{2.5} \geq 75\text{th percentile}$ ($24.0 \mu\text{g}/\text{m}^3$) (table 5).

In general population sample, no data from monitoring stations was available for PISA1, PISA2 and SEASD studies. The overall annual mean concentrations of air pollutants were $41.5 \mu\text{g}/\text{m}^3$ O_3 , $42.8 \mu\text{g}/\text{m}^3$ NO_2 , $40.7 \mu\text{g}/\text{m}^3$ PM_{10} ; $\text{PM}_{2.5}$ concentration was not routinely monitored during the period of the studies (table 5). Considering the EU reference values of air pollutants concentration, 36.2% of the European general population samples were exposed to $\text{NO}_2 \geq 40 \mu\text{g}/\text{m}^3$, no sample was exposed to $\text{PM}_{10} \geq 40 \mu\text{g}/\text{m}^3$. Considering the WHO Air Quality guidelines for air pollutants concentration, 36.2% of the European general population samples were exposed to $\text{NO}_2 \geq 40 \mu\text{g}/\text{m}^3$, 100.0% to $\text{PM}_{10} \geq 20 \mu\text{g}/\text{m}^3$ (table 5). Considering the 75th percentile of air pollutants concentration, 50.0% of the European general population samples were exposed to $\text{O}_3 \geq 75\text{th percentile}$ ($48.7 \mu\text{g}/\text{m}^3$)

and $PM_{10} \geq 75$ th percentile ($42.3 \mu\text{g}/\text{m}^3$); no general population sample was exposed to $NO_2 \geq 75$ th percentile (table 5).

With regards to the indoor/outdoor pollutants concentration at school, data were available only in CCM and EDEN studies. The prevalence rates of exposed subjects were 48.1% to indoor $PM_{2.5}$ at school $\geq 25 \mu\text{g}/\text{m}^3$ (EU level), 95.4% to indoor $PM_{2.5}$ at school $\geq 10 \mu\text{g}/\text{m}^3$ (WHO level), 34.1% to outdoor $PM_{2.5}$ at school $\geq 25 \mu\text{g}/\text{m}^3$ (EU level), 91.5% to outdoor $PM_{2.5}$ at school $\geq 10 \mu\text{g}/\text{m}^3$ (WHO level). In EDEN study the prevalence rates of subjects exposed to indoor PM_{10} at school $\geq 20 \mu\text{g}/\text{m}^3$ (WHO level) was 42.0%, to outdoor $PM_{2.5}$ at home $\geq 25 \mu\text{g}/\text{m}^3$ (EU level) 30.3%, to outdoor $PM_{2.5}$ at home $\geq 10 \mu\text{g}/\text{m}^3$ (WHO level) 93.7% (table 6).

CCM study had information about dust allergens concentration inside classroom: 25.3% of children were exposed to dog allergens ≥ 75 th percentile ($13.33 \text{ ng}/\text{m}^3$), 25.3% to cat allergens (75th percentile: $9.5 \text{ ng}/\text{m}^3$) and 25.0% to mites allergens (75th percentile: $2.03 \text{ ng}/\text{m}^3$) (table 6).

Prevalence of disease outcomes/biomarkers in subjects exposed to allergens and to environmental pollution

"Independent effect"

Children samples

Tables 7-12 and 18 report the results of the chi-square test aimed at assessing the association between disease outcomes/biomarkers and exposure to allergens and environmental pollution. Results of the cumulative analyses on children subsample of the HEALS database are shown in table 18; different and additional results coming from the individual studies were assessed.

Host risk factors

A significantly higher prevalence of almost all the disease outcomes/biomarkers was shown in subjects with asthma/allergic rhinitis familiarity with respect to subjects without familiarity, in particular for asthma (16.5% vs 8.3%), eczema (26.8% vs 20.1%), AR diagnosis (27.5% vs 16.8%), AR symptoms (40.5% vs 30.5%) and SPT positivity (48.3% vs 32.3%); a significantly lower prevalence was found for dry cough (30.0% vs 35.5%) and severe AR (63.4% vs 73.4%) (table 18). Moreover, a significantly higher prevalence of wheeze (35.8% vs 22.6%) and dry cough (11.0% vs 6.8%) was found in CCM study (table 7).

Childhood respiratory infections were associated with significantly higher prevalence of wheeze (54.8% vs 30.4%), dry cough (51.1% vs 48.9%), AR symptoms (38.6% vs 29.4%) and SPT positivity (44.5% vs 35.9%), with a borderline higher prevalence of asthma (17.3% vs 14.7%) and with a significantly lower prevalence of eczema (19.9% vs 28.8%), AR diagnosis (18.0% vs 44.0%) and severe AR (54.8% vs 71.9%) (table 18). Conversely, a higher prevalence was found in CCM study for the same outcomes (18.4% vs 13.7%, 11.5% vs 7.0%, 50.6% vs 39.7%, respectively) (table 7).

Environmental risk factors

As regards the exposure to allergens, subjects exposed to mould, with respect to subjects not exposed, had a significantly higher prevalence of wheeze (55.6% vs 47.7%), dry cough (42.2% vs 31.9%), eczema (20.0% vs 17.4%), AR diagnosis (10.6% vs 8.3%) and AR symptoms (36.8% vs 30.8%) and a borderline higher prevalence of asthma (8.8% vs 6.8%) (table 18).

Pets exposure, with respect to non exposure, was related to a significantly higher prevalence of asthma (11.9% vs 7.7%), eczema (22.9% vs 19.1%), AR diagnosis (29.7% vs 11.1%) and severe AR (71.9% vs 58.8%); a significantly lower prevalence of wheeze (42.5% vs 50.9%) and dry cough (24.6% vs 35.6%) and a borderline lower prevalence of AR symptoms (30.4% vs 32.8%) (table 18); a borderline higher prevalence of AO (1.6% vs 0.7%) was found in CCM study (table 7).

Subjects exposed to cockroaches, with respect to subjects not exposed, had a significantly higher prevalence of wheeze (36.6 % vs 30.2%), dry cough (13.2% vs 7.3%) and AR symptoms (34.0% vs 28.0%) (table 18); a significantly higher prevalence of severe AR (57.5% vs 41.2%) in CCM study (table 7) and a borderline higher prevalence of specific IgE (22.5% vs 14.7%) in EDEN study were found (table 9).

Presence of carpets at home, with respect to absence, was related to a significantly lower prevalence of asthma (4.9% vs 7.3%), wheeze (37.9% vs 53.8%), dry cough (24.4% vs 37.2%), AR diagnosis (6.7% vs 8.7%), AR symptoms (28.2% vs 33.5%), SPT positivity (33.5% vs 41.3%) (table 18) and, on the contrary, to a borderline higher prevalence of asthma in REPRO_PL study (20.0% vs 4.1%) (table 10).

As regards the exposure to sources of air pollutants, children exposed to passive smoke, with respect to those not exposed, showed significantly higher prevalence of asthma (10.0% vs 8.9%), wheeze (55.0% vs 40.5%), dry cough (40.2% vs 26.0%), AR diagnosis (19.6% vs 16.0%), AR symptoms (33.7% vs 30.6%), severe AR (74.2% vs 63.4%) and a significantly lower prevalence of severe asthma (21.1% vs 37.3%) (table 18).

Presence of air pollution sources near home, with respect to absence, was related to significantly higher prevalence of wheeze (26.9% vs 11.3%), AR diagnosis (8.2% vs 4.4%) and AR symptoms (28.6% vs 14.7%) (table 18).

Presence of air pollution sources near school, with respect to absence, was related to a significantly higher prevalence of asthma (8.1% vs 5.4%), wheeze (28.7% vs 23.0%) and AR diagnosis (9.5% vs 6.0%), to a borderline higher prevalence of SPT positivity (40.0% vs 34.4%) and to a significantly lower prevalence of AO (0.6% vs 1.9%) in CCM study (table 7).

As regards the measured PM_{2.5} school indoor concentration, children exposed to indoor concentration $\geq 25 \mu\text{g}/\text{m}^3$, with respect to those not exposed, had a significantly lower prevalence of asthma (11.5% vs 15.0%), eczema (21.3% vs 26.5%), AR diagnosis (22.7% vs 39.2%) and severe AR (59.1% vs 71.0%) (table 18); on the contrary, a significantly higher prevalence of eczema (16.5% vs 12.0%) in CCM study (table 7) and a borderline higher prevalence of wheeze (47.2% vs 40.6%) in EDEN study were found (table 9).

Children exposed to PM_{2.5} school outdoor concentration $\geq 25 \mu\text{g}/\text{m}^3$, with respect to those not exposed, showed a significantly higher prevalence of wheeze (36.2% vs 31.7%) and a significantly lower prevalence of dry cough (4.9% vs 8.2%) and AR diagnosis (33.3% vs 38.5%) (table 18); a significantly higher prevalence of eczema (17.3% vs 12.6%) and a borderline lower prevalence of severe AR (37.3% vs 50.0%) were found in CCM study (table 7).

In EDEN study, the PM₁₀ school indoor concentration was measured; children exposed to concentrations $\geq 20 \mu\text{g}/\text{m}^3$, with respect to those not exposed, showed a higher prevalence of wheeze (48.7% vs 40.9%) and AR diagnosis (85.6% vs 80.0%) (table 9).

Dust allergens concentration inside classroom was measured within CCM study; no significant association with disease outcomes/biomarkers was found (table 7).

Table 20a reports the prevalence of respiratory outcomes in subjects exposed to air pollutants concentration levels higher than 75th percentile. Overall, the bivariate analyses showed a significantly higher prevalence of respiratory outcomes in subjects exposed to air pollutants concentration levels < 75th percentile, with respect to those exposed to levels ≥ 75 th percentile. However, subjects exposed to NO₂ levels ≥ 75 th percentile showed a significantly higher prevalence of asthma (26.8% vs 10.2%), eczema (29.7% vs 19.8%) and severe asthma (52.8% vs 18.3%). With regard to the air pollutants concentration clusters ("air pollutants cluster"), subjects exposed to only NO₂ concentration ≥ 75 th percentile, with respect to those exposed to only O₃ concentration ≥ 75 th percentile and to those exposed to PM₁₀&PM_{2.5} concentration ≥ 75 th percentile, showed a significantly higher prevalence of asthma (32.5% vs 10.0% vs 12.0%), eczema (35.3% vs 21.8% vs 12.3%), AR diagnosis (24.6% vs 19.5% vs 9.8%), AR symptoms (39.1% vs 32.7% vs 31.7%) and severe asthma (52.8% vs 18.3% vs 0.0%); subjects exposed to only O₃ concentration ≥ 75 th percentile, with respect to those exposed to only NO₂ concentration ≥ 75 th percentile and to those exposed to PM₁₀&PM_{2.5} concentration ≥ 75 th percentile, showed a significantly higher prevalence of wheeze (51.8% vs 28.6% vs 19.6%), dry cough (38.2% vs 8.5% vs 21.8%) and severe AR (74.0% vs 33.3% vs 49.3%) (table 20a).

General population sample

Tables 13-17 and 19 report the results of the chi-square test aimed at assessing the association between disease outcomes/biomarkers and exposure to allergens and environmental pollution in general population samples. In particular, results about the cumulative analyses on general population subsample of the HEALS database are shown in table 19; different and additional results coming from the individual studies were assessed.

Host risk factors

A significantly higher prevalence of all the disease outcomes was shown in subjects with asthma/allergic rhinitis familiarity with respect to subjects without familiarity: asthma (13.6% vs 6.3%), wheeze (31.0% vs 20.6%), dry cough (19.5% vs 16.0%), eczema (14.6% vs 10.1%), AR diagnosis (30.8% vs 19.3%) (table 19); severe asthma (12.3% vs 6.2%), severe AR (24.1% vs 13.5%), AO (16.0% vs 9.3%) and SPT positivity (36.9% vs 31.4%) in PISA2 study (table 14).

The same results were found for childhood respiratory infections and significantly higher prevalence of: asthma (13.2% vs 4.9%), wheeze (30.7% vs 19.1%), dry cough (19.3% vs 15.2%), eczema (13.4% vs 9.9%), AR symptoms (23.8% vs 19.5%) (table 19); severe asthma (13.1% vs 4.6%), severe AR (18.8% vs 13.3%), AO (14.8% vs 8.1%) and BHR (35.2% vs 24.8%) in PISA2 study (table 14).

Environmental risk factors

As regards pets exposure, no significant association was found, except for a higher prevalence of BHR (31.5% vs 24.2%) in PISA2 study (table 14).

As regards the exposure to sources of air pollutants, subjects exposed to passive smoke, with respect to those not exposed, showed significantly higher prevalence of AR diagnosis (21.0% vs 17.5%) and significantly lower prevalence of wheeze (20.4% vs 24.4%), eczema (13.2% vs 15.1%) and AO (10.8% vs 16.9%) (table 19); a higher borderline prevalence of severe AR (16.0% vs 13.6%) and dry cough (12.7% vs 4.7%) in PISA2 (table 14) and in SEASD study (table 16), respectively; subjects exposed to passive smoke showed a borderline lower prevalence of blood eosinophilia (1.7% vs 5.9%) in SEASD study (table 16).

Presence of vehicular traffic near home, with respect to absence, was related to significantly higher prevalence of eczema (16.2% vs 13.8%) and AO (16.6% vs 12.0%) and borderline higher prevalence of asthma (8.4% vs 6.9%), wheeze (26.4% vs 23.6%) and dry cough (19.0% vs 16.4%) (table 19); significantly higher prevalence of severe AR (16.3% vs 13.5%) and borderline higher prevalence of severe asthma (8.0% vs 6.1%) were found in PISA2 study (table 14); a significantly higher prevalence of AR symptoms (40.3% vs 34.0%) in IMCA study (table 15).

Work exposure to fume/gas/dust, with respect to not exposure, was related to significantly higher prevalence of asthma (8.0% vs 6.4%), wheeze (27.3% vs 15.7%), dry cough (22.0% vs 11.8%), eczema (14.9% vs 11.9%), AR diagnosis (19.7% vs 16.6%) and AO (19.1% vs 10.1%) (table 19); significantly higher prevalence of AR symptoms (43.3% vs 33.0%) in IMCA study (table 15).

In PISA2 study, the effect of air pollution sources near home and of living $\leq 100\text{m}$ from a main road was assessed; significantly higher prevalence of asthma (8.4% vs 5.7%), wheeze (26.5% vs 22.2%), dry cough (19.2% vs 15.3%), AR diagnosis (22.3% vs 18.1%), severe asthma (8.2% vs 5.5%) and severe AR (16.7% vs 12.4%) were found in subjects exposed to air pollution sources near home, with respect to subjects not exposed (table 14); significantly higher prevalence of asthma (9.7% vs 6.0%), wheeze (27.4% vs 23.0%) and severe asthma (9.2% vs 5.9%) were found in subjects living $\leq 100\text{m}$ from a main road, with respect to subjects living $> 100\text{m}$ (table 14).

"Combined effect"

Children sample

Table 20b reports the prevalence of respiratory outcomes in subjects characterized by different clusters of exposure ("combined exposure cluster"). Significantly higher prevalence rates of all the health outcomes were shown in cluster 1 ("children exposed to only allergens") with respect to cluster 3 ("children with asthma/allergic disease familiarity and exposed to allergens and high levels of PM₁₀, PM_{2.5}, NO₂") and cluster 2 ("children with asthma/allergic disease familiarity and exposed to allergens and high level of O₃ concentration"): 10.0% vs 6.6% vs 8.0% for asthma, 54.9% vs 26.5%

vs 18.0% for wheeze, 40.3% vs 8.4% vs 8.7% for dry cough, 22.0% vs 17.8% vs 16.0% for eczema, 20.1% vs 8.9% vs 7.5% for AR diagnosis, 33.6% vs 30.3% vs 24.9% for AR symptoms.

Allergenic and environmental risk factors for disease outcomes/biomarkers: results of logistic regression analyses

"Independent effect"

Children sample

Tables 21a, 22, 23a, 24a, 25, 31a-c, 32a-c, 34a-c report the results of the multivariable logistic regression analyses performed to assess the effect of environmental and host risk factors on disease outcomes/biomarkers. Table B summarizes the main results of the logistic regression analysis performed on the individual studies and on cumulative data.

Host risk factors

Logistic regression analysis confirmed a significantly higher risk of having asthma/allergic diseases in subjects with asthma/allergic diseases familiarity: for asthma (OR ranging from 3.17 to 5.96) (tables 32a, 21a), wheeze (OR ranging from 1.53 to 1.97) (tables 34b, 34c, 31a), dry cough (OR ranging from 1.38 to 2.13) (tables 34b, 34c, 21a), eczema (OR ranging from 1.32 to 1.93) (tables 25, 22), AR diagnosis (OR ranging from 1.74 to 6.11) (tables 25, 21a), AR symptoms (OR ranging from 1.51 to 2.64) (tables 25, 31a), severe AR (OR 2.69) (table 21a) and SPT positivity (OR ranging from 2.09 to 2.17) (tables 31a, 21a).

Childhood infections were a significant risk factor for asthma (OR ranging from 5.15 to 6.41) (tables 32a, 21a), wheeze (OR ranging from 6.59 to 7.55) (tables 32a, 21a), dry cough (OR 2.11) (table 21a), AR diagnosis (OR 2.58) (table 21a) and AR symptoms (OR ranging from 1.70 to 2.14) (tables 32a, 21a).

Environmental risk factors

As regards the allergens exposure, moulds resulted a significant risk factor for dry cough (OR ranging from 1.25 to 2.56) (tables 25, 21a), eczema (OR 1.26) (table 25) and AR symptoms (OR ranging from 1.19 to 1.68) (tables 25, 21a); a borderline risk value was found for wheeze (OR 1.13) (table 25) and AR diagnosis (OR 1.23) (table 25).

Pets exposure showed a significant negative association with dry cough (OR 0.57) (table 31a) and AR symptoms (OR ranging from 0.73 to 0.68) (tables 31a, 32a).

Cockroaches exposure resulted a significant risk factor for dry cough (OR 1.54) (table 31a) and severe AR (OR 3.76) (table 21a); a significant negative association with asthma (OR 0.39) (table 21a) and a borderline negative association with eczema (OR 0.56) (table 21a) were found.

Significant negative associations between carpets presence at home and asthma (OR ranging from 0.39 to 0.37) (tables 31a, 21a), wheeze (OR ranging from 0.61 to 0.64) (tables 21a, 31a), AR diagnosis (OR 0.65) (table 31a) and SPT positivity (OR 0.68) were shown (table 31a).

Exposure to at least one indoor allergen (i.e. pets or cockroaches or carpets or moulds) was shown as a risk factor for dry cough (OR 1.23), AR diagnosis (OR 1.22) and AR symptoms (OR 1.13) (tables 34b, 34c).

With regards to the exposures to air pollution sources, passive smoke exposure (a source of indoor PM) was a significant risk factor for wheeze (OR ranging from 1.23 to 1.45) (tables 25, 32c), dry cough (OR 1.17) (table 25), AR diagnosis (OR 1.41) (table 32c), AR symptoms (OR ranging from 1.31 to 1.36) (tables 31c, 32c).

Living within 100m from main roads showed a significant negative association with SPT positivity (OR 0.66) (table 21a) and a borderline negative association with eczema (OR 0.67) in CCM study (table 21a).

Sources of air pollution near home and near school resulted significant risk factors for disease outcomes. Sources near home were a borderline risk factor for eczema (OR 1.91) (table 24a); sources near school were a significant risk factor for AR diagnosis (OR 4.35) (table 21a) and a borderline risk factor for asthma (OR 2.76) (table 21a).

With regards to the measured PM_{2.5} school indoor concentration, children exposed to indoor concentration $\geq 25 \mu\text{g}/\text{m}^3$ had a significantly higher risk of having eczema (OR 1.98) (table 21a).

Children exposed to PM_{2.5} school outdoor concentration $\geq 25 \mu\text{g}/\text{m}^3$ had a significantly higher risk of having wheeze (OR ranging from 1.57 to 1.91) (tables 32a, 21a) and a borderline higher risk of having asthma (OR 1.68) (table 23a); a significant negative association with SPT positivity (OR 0.62) and a borderline negative association with dry cough (OR 0.54) were found (table 21a).

With regards to the air pollutants concentration within city, children exposed to high O₃ concentration levels (≥ 75 th percentile) had a lower significant risk of having asthma (OR 0.54) (table 32b), wheeze (OR ranging from 0.38 to 0.34) (tables 32b, 31b), eczema (OR ranging from 0.60 to 0.50) (tables 32b, table 34b) and AR diagnosis (OR 0.46) (table 32b); on the contrary O₃ exposure was a risk factor for AR symptoms (OR 1.95) (table 34b). Exposure to high NO₂ levels showed a significant negative association with wheeze (OR 0.55) (table 31b), eczema (OR ranging from 0.63 to 0.53) (tables 31b, 34b), severe AR (OR 0.43) (table 32b) and a significant positive association with AR symptoms (OR ranging from 1.27 to 2.46) (tables 32b, 34b). Exposure to high PM_{2.5} levels showed a significant positive association with severe AR (OR 3.20) (table 32b) and a borderline negative association with asthma (OR 0.54) and AR diagnosis (OR 0.56) (table 32b).

Considering the different clusters of air pollutants exposure ("air pollutants cluster"), the exposure to high level of only PM, with respect to the exposure to high level of only O₃, showed a significant negative association with AR diagnosis (OR 0.50) (table 32c); the exposure to high level of only NO₂, with respect to the exposure to high level of only O₃, showed a significant positive association with AR symptoms (OR 1.31) (table 34c) and a negative association with severe AR (OR 0.43) (table 32c).

General population sample

Tables 26-30, 33 report the results of the multivariable logistic regression analyses performed to assess the effect of environmental and host risk factors on disease outcomes/biomarkers. Table C summarizes the main results of the logistic regression analysis performed on the individual studies and on cumulative data.

Host risk factors

Logistic regression analysis confirmed a significantly higher risk of having asthma/allergic diseases in subjects with asthma/allergic diseases familiarity: for asthma (OR ranging from 2.30 to 7.23) (tables 27, 29), wheeze (OR ranging from 1.69 to 4.83) (tables 27, 29), dry cough (OR 3.24) (table 29), eczema (OR ranging from 1.56 to 3.64) (tables 27, 29), AR diagnosis (OR 1.87) (table 27), severe asthma (OR 2.29) (table 27), severe AR (OR 1.88) (table 27) and AO (OR 2.58) (table 27); a borderline risk value was found for SPT positivity (OR 1.31) (table 27).

Childhood infections were a significant risk factor for asthma (OR ranging from 2.95 to 3.19) (tables 27, 29), wheeze (OR ranging from 1.87 to 3.30) (tables 27, 29), dry cough (OR 1.57) (table 30), AR diagnosis (OR 1.39) (table 27), severe asthma (OR 2.88) (table 27), severe AR (OR 1.52) (table 27), AO (OR 2.07) (table 27) and BHR (OR 1.73) (table 27); a borderline risk value was found for eczema (OR 1.34) (table 27).

Environmental risk factors

With regards to allergens exposure, only information about pets exposure at home were available, but no significant association was found with disease outcomes/biomarkers.

With regards to the exposure to air pollution sources, passive smoke exposure resulted a significant risk factor for AR symptoms (OR 1.44) (table 28) and a borderline risk factor for AR diagnosis (OR 1.25) (table 27) and blood eosinophilia (OR 1.90) (table 27); a significant negative association with SPT positivity (OR 0.66) was found (table 27).

Living within 100m from main roads was a significant risk factor for asthma (OR 1.54) and severe asthma (OR 1.51) (table 27).

Sources of air pollution near home were significant risk factors for disease outcomes, in particular for wheeze (OR 1.29) (table 26), dry cough (OR 1.30) (table 26), AR diagnosis (OR 1.36)

(table 26) and severe AR (OR 1.32) (table 27). A borderline risk value was found for SPT positivity (OR 1.22) (table 27).

The presence of vehicular traffic near home was significantly associated with asthma (OR 1.30) (table 33) and it showed a borderline significance for eczema (OR 1.17) (table 33); a negative association was found with AO (OR 0.60) (table 28).

Finally, in general population sample, work exposure to fume/gas/dust resulted an important risk factor for all disease outcomes: for asthma (OR 1.42) (table 26), wheeze (OR 1.50) (table 26), dry cough (OR 1.49) (table 26), eczema (OR ranging from 1.45 to 1.64) (tables 33, 28), AR diagnosis (OR ranging from 1.32 to 1.87) (tables 33, 28) and AR symptoms (OR 1.39) (table 28); a borderline association was found with AO (OR 1.28) (table 33).

Effect of allergens and air pollution combined exposure

"Combined effect"

Children sample

1) *First statistical approach*: tables 21b, 23b, 24b, 31d, 32d report the results of the multivariable logistic regression analyses performed with interaction terms to assess the effect of the combined exposure to allergens and air pollution with respect to the single exposure to allergens or to air pollution. Table D summarizes the main results of the logistic regression analyses performed on individual studies and on cumulative data.

In particular, results of the significant combined exposures are described.

Environmental risk factors

In CCM study, the combined exposure to pets and to school indoor $PM_{2.5} \geq 25 \mu g/m^3$ significantly increased the risk of asthma with respect to only pets or only indoor $PM_{2.5}$ exposure (from OR 0.62 for only pets exposure to OR 1.70 for combined exposure to pets and indoor $PM_{2.5}$; from OR 0.67 for only indoor $PM_{2.5}$ exposure to OR 1.89 for combined exposure to indoor $PM_{2.5}$ and pets) (table 21b). On the contrary, in the cumulative analysis on CCM and EDEN studies a significant decrease of the risk of AR symptoms in children exposed to both pets and school indoor $PM_{2.5}$ with respect to those exposed to only indoor $PM_{2.5}$ was shown (from OR 0.80 to OR 0.20) (table 32d).

The combined exposure to carpets and school indoor $PM_{2.5} \geq 25 \mu g/m^3$ significantly reduced the risk of dry cough with respect to only indoor $PM_{2.5}$ exposure (from OR 1.08 for only indoor $PM_{2.5}$ exposure to OR 0.45 for combined exposure) (table 21b); on the contrary, the combined exposure to carpets and school outdoor $PM_{2.5} \geq 25 \mu g/m^3$ significantly increased the risk of wheeze with respect to only outdoor $PM_{2.5}$ exposure (from OR 0.93 for only outdoor $PM_{2.5}$ exposure to OR 2.01 for combined exposure) (table 21b).

Another important interaction was found between mould and school outdoor $PM_{2.5}$; indeed, the combined exposure significantly increased the risk of eczema with respect to only mould or only outdoor $PM_{2.5}$ exposure (from OR 0.93 for only mould exposure to OR 2.36 for combined exposure and from OR 1.10 for only outdoor $PM_{2.5}$ exposure to OR 2.89 for combined exposure) (table 21b).

2) *Second statistical approach*: tables 31e1, 31e2, 32e1, 32e2, 34d1, 34d2 report the results of the multivariable logistic regression analyses stratified by the concentration values of air pollutants below and above the 75th percentile to assess the effect of the combined exposure to allergens and to high concentrations of air pollutants. Tables E1-E7 summarizes the main results of the logistic regression analyses performed on individual studies and on cumulative data.

Host risk factors

Overall, asthma/allergic rhinitis familiarity and childhood respiratory infections were confirmed as risk factors for all health outcomes, with higher risk in children exposed to high concentrations of air pollutants than in those exposed to low concentrations of air pollutants (OR values ranging on the basis on the considered outcome and air pollutant; see tables 31e1, 31e2, 32e1, 32e2, 34d1, 34d2).

Environmental risk factors

The effect of passive smoke exposure was higher in children exposed to high concentrations of air pollutants than in those exposed to low concentrations of air pollutants for wheeze (OR 2.26 vs 1.25 for O₃ concentration; OR 1.51 vs 1.27 for NO₂; OR 1.96 vs 1.26 for PM₁₀; OR 1.61 vs 1.34 for PM_{2.5}) (table 34d1). The effect was significant in children exposed to low concentrations of air pollutants for AR diagnosis (OR 1.85 for NO₂, OR 1.63 for PM₁₀ and OR 1.52 for PM_{2.5}) (table 32e2) and AR symptoms (OR 1.39 for O₃) (table 31e2); it was significant in children exposed to high concentrations of air pollutants for AR symptoms (OR 1.46 for NO₂) and SPT (OR 1.65 for O₃) (table 31e2). On the contrary, there was a negative association between passive smoke exposure and eczema only in children exposed to high concentrations of air pollutants (OR 0.49 for NO₂, OR 0.38 for PM₁₀ and OR 0.48 for PM_{2.5}) (table 32e2, 31e2)

The effect of the exposure to at least one indoor biological allergen was significant in children exposed to low concentrations of air pollutants for dry cough (OR 1.26 for O₃, OR 1.24 for NO₂, OR 1.23 for PM₁₀), for AR diagnosis (OR 1.24 for O₃, OR 1.21 for NO₂, OR 1.22 for PM₁₀), for AR symptoms (OR 1.15 for O₃, OR 1.11 for NO₂, OR 1.11 for PM₁₀) (tables 34d1, 34d2). Allergens exposure showed a negative association with wheeze in children exposed to high concentration of O₃ (OR 0.56) and low concentration of PM_{2.5} (OR 0.80) (table 34d1).

Considering the individual biological allergen, the effect of moulds exposure was significant in children exposed to high concentrations of air pollutants for eczema (OR 2.42 for PM_{2.5}) and AR symptoms (OR 1.65 for NO₂) (table 31e2). The effect was significant in children exposed to low concentrations of air pollutants for wheeze (OR 1.42 for O₃), dry cough (OR 1.86 for NO₂), eczema (OR 1.88 for O₃) and AR symptoms (OR 1.55 for O₃ and 1.39 for PM₁₀) (tables 31e1, 31e2).

The effect of pets exposure was significant in children exposed to high concentrations of NO₂ for asthma (OR 2.07) and in those exposed to low concentrations of air pollutants for AR diagnosis (OR 1.78 for O₃, OR 1.62 for NO₂, OR 1.60 for PM₁₀, OR 1.50 for PM_{2.5}) (tables 32e1, 32e2). A negative association with dry cough (OR 0.50 for O₃, OR 0.55 for NO₂, OR 0.59 for PM₁₀, OR 0.44 for PM_{2.5}) (table 31e1) and AR symptoms (OR 0.63 for NO₂ and 0.75 for PM₁₀) (table 31e2) was found in children exposed to low concentrations of air pollutants; a negative association with AR symptoms was found in children exposed to high concentrations of O₃ (OR 0.45) (table 31e2).

The effect of cockroaches exposure was significant in children exposed to low concentrations of O₃ (OR 2.14) and PM_{2.5} (OR 2.32) for dry cough (table 31e1); it was significant in children exposed to high concentrations of air pollutants for dry cough (OR 2.44 for NO₂, OR 2.80 for PM₁₀, OR 2.27 for PM_{2.5}), AR diagnosis (OR 2.88 for PM₁₀ and OR 2.53 for PM_{2.5}) (tables 31e1, 31e2) and severe AR (OR 3.24 for PM_{2.5}) (table 32e2).

Overall, the effect of carpets exposure showed a negative association with asthma (OR 0.43 for O₃, OR 0.35 for NO₂, OR 0.32 for PM₁₀, OR 0.34 for PM_{2.5}), wheeze (OR 0.60 for NO₂, OR 0.54 for PM₁₀, OR 0.53 for PM_{2.5}), AR diagnosis (OR 0.60 for O₃, OR 0.57 for NO₂) and SPT (OR 0.60 for NO₂, OR 0.63 for PM₁₀, OR 0.62 for PM_{2.5}) in children exposed to low level of air pollutants concentrations; a negative association was found with asthma (OR 0.35 for O₃, OR 0.39 for NO₂), wheeze (OR 0.38 for O₃) and SPT (OR 0.52 for O₃) in children exposed to high levels of air pollutants (tables 31e1, 31e2).

With regards to the air pollution sources exposure, the effect of exposure near home was significant in children exposed to high concentration of NO₂ for wheeze (OR 5.37) (table 31e1); the effect of exposure to school PM_{2.5} indoor concentration $\geq 25 \mu\text{g}/\text{m}^3$ was significant in children exposed to high concentration of O₃ for eczema (OR 2.20) and it showed a negative association with wheeze (OR 0.69) in those exposed to low concentration of O₃ (tables 32e1, 32e2).

3) *Third statistical approach*: Tables 31f1, 31f2, 32f1, 32f2, 34e1, 34e2 report the results of the multivariable logistic regression analyses stratified by the levels of the “air pollutants cluster” (cluster 1: only NO₂ \geq 75th percentile; cluster 2: only O₃ \geq 75th percentile; cluster 3: PM₁₀ & PM_{2.5} \geq 75th percentile) to assess the effect of the combined exposure to allergens and to different combinations of air pollutants. Tables E1-E7 summarizes the main results of the logistic regression analyses performed on individual studies and on cumulative data.

Host risk factors

On the whole, asthma/allergic rhinitis familiarity was confirmed as risk factor for all the health outcomes, with risk values ranging on the basis of the considered outcomes and cluster levels; see tables 31f1, 31f2, 32f1, 32f2, 34e1, 34e2. Childhood infections confirmed their effect as risk factor only for asthma, wheeze and AR symptoms (tables 32f1, 32f2).

Environmental risk factors

Exposure to passive smoke was a significant risk factor in cluster 2 and cluster 3 for wheeze, respectively (cluster 2: OR ranging from 1.28 to 1.70; cluster 3: OR ranging from 1.96 to 2.13) (tables 34e1, 31f1); a significant risk was found in cluster 2 for AR diagnosis (OR 1.79) (table 32f2). Passive smoke showed a negative association with eczema in cluster 3 (OR 0.38) (tables 31f2, 32f2).

The exposure to at least one indoor biological allergen was a significant risk factor in cluster 2 for dry cough (OR 1.23), AR diagnosis (OR 1.23) and AR symptoms (OR 1.12) (tables 34e1, 34e2). In particular, pets exposure showed a negative association with dry cough (OR 0.50) and AR symptoms (OR ranging from 0.58 to 0.60) (tables 31f2, 32f2) in cluster 2; cockroaches was a significant risk factor for dry cough (OR 2.80) (table 31f1) and AR diagnosis (OR 2.88) (table 31f2) in cluster 3; carpets exposure showed a negative association with asthma (OR 0.09 and OR 0.42) in cluster 1 and 2, with wheeze (OR 0.57) and SPT (OR 0.63) in cluster 2 (tables 31f1, 31f2).

4) *Fourth statistical approach*: table 34f report the results of the multivariable logistic regression analyses with “combined exposure cluster” as independent variable and adjusting for sex, age and study attendance. In particular the following clusters were analyzed: cluster 1: subjects exposed to only allergens; cluster 2: subjects with asthma/allergic disease familiarity and exposed to allergens and high level of O₃ concentration (\geq 75th percentile); cluster 3: subjects with asthma/allergic disease familiarity and exposed to allergens and high levels of air pollutants concentration (\geq 75th percentile) (PM₁₀, PM_{2.5}, NO₂). Logistic regression analyses, performed taking into account cluster 1 as reference category, showed cluster 2 and 3 as significant risk factors for eczema (OR 1.41 and OR 1.34, respectively); cluster 2 a positive association with wheeze (OR 1.25) and a negative association with dry cough (OR 0.71), AR diagnosis (OR 0.63) and AR symptoms (OR 0.70).

SUMMARY OF THE RESULTS AND DISCUSSION

The HEALS database allowed to perform statistical analyses at different detail level (from Step 1 – individual study - to Step 3 –children entire sample) and different statistical approaches to assess the effect of combined exposure to biological allergens and air pollutants. The results, accounting for few inconsistencies, showed a clear relationship between asthma/allergic diseases and environmental exposure. They will need to be considered in the statistical analyses of the EXHES data (WP17) and during the development of protocols and guidelines for the setting up of large European environment and health examination surveys.

Frequency of investigated outcomes and allergens/pollutants exposure

The prevalence of asthma and allergic diseases in HEALS database is in line with that of other European studies (Baldacci et al 2015), with values ranging from 12.5% in children to 7.0% in general population for asthma and from 33.0% in children to 37.5% in general population for allergic rhinitis symptoms.

HEALS database contains information about the main risk factors for asthma and allergic diseases: sources of exposure to PM and biological allergens and direct measurements of air pollutants concentration (Baldacci et al 2015). Over 20% of the children were exposed to biological allergens (24.6% at mould, 19.9% at pets, 22.1% at carpets). An elevated exposure to air pollution was shown: 77.7% to air pollution sources near home, 89.6% to vehicular traffic near home, 48.1% to PM_{2.5} indoor concentration level \geq 25 $\mu\text{g}/\text{m}^3$ at school and 34.1% to PM_{2.5} outdoor concentration level \geq 25 $\mu\text{g}/\text{m}^3$ at school. As regards general population sample, 47.4% of subjects were exposed to

pets and 50-60% were exposed to air pollution sources: 61.8% to air pollution sources near home, 48.9% to vehicular traffic near home.

Considering the EU reference values of air pollutants concentration, pollution monitoring stations data (EDMS database) showed that 80% of children were exposed to values $\geq 40 \mu\text{g}/\text{m}^3$ of NO_2 , 10.8% were exposed to values $\geq 25 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ and no child was exposed to values $\geq 40 \mu\text{g}/\text{m}^3$ of PM_{10} . As regards the general population sample, 36.2% were exposed to values $\geq 40 \mu\text{g}/\text{m}^3$ of NO_2 and no subject was exposed to values $\geq 40 \mu\text{g}/\text{m}^3$ of PM_{10} . Considering these results (i.e. low concentration levels of PM within cities) and that no threshold for PM has been identified below which no damage to health is observed ([http://www.who.int/en/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](http://www.who.int/en/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)), it was decided to use a cut-off corresponding to the 75th percentile of air pollutants concentration for assessing people exposure: about 20% of the European children sample were exposed to values ≥ 75 th percentile of air pollutants concentration (23.1% for O_3 , 28.6% for NO_2 , 21.4% for PM_{10} and 20.0% for $\text{PM}_{2.5}$); about 50% of the European general population sample were exposed to values ≥ 75 th percentile of air pollutants concentration (50.0% for O_3 and for PM_{10}).

Allergenic and environmental risk factors for disease outcomes/biomarkers

"Independent effect"

Through logistic regression analyses asthma/allergic disease familiarity (a proxy of hereditary genetic factors) and passive smoke exposure were shown as important risk factors both in children sample and in general population sample; moreover, work exposure to fume/gas/dust resulted an important risk factor for asthmatic and allergic diseases/symptoms in adult subjects. These results are in line with other scientific evidences (Baldacci et al 2015, Maio et al 2016, WHO 2007, Thurston et al 2017).

The role of early childhood infections and immunization in the development of allergic and asthma diseases remains controversial (Thomson et al 2010, Resch et al 2004). Our data showed that childhood infections are risk factors for asthma and allergic diseases/symptoms both in children sample and in general population sample; contrasting results were found for AR diagnosis.

Exposure to biological allergens may produce respiratory infections, sensitization, respiratory allergic diseases and wheezing (Baldacci et al 2015, Gold et al 2017). The HEALS data showed that exposure to moulds at home was an important risk factor for asthmatic and allergic diseases/symptoms in children, in line with other scientific evidences (Baldacci et al 2015).

Controversial results were found for pets and cockroaches.

Pets showed a positive association with AR diagnosis and a negative association with dry cough and AR symptoms; other scientific studies showed the same controversial results with findings that may vary according to the type of pet and to the individuals' allergic sensitization (Baldacci et al 2015, Gergen et al 2018, Gold et al 2017). Such results may partly be due to different study designs, type of exposure, health outcome (Almqvist et al 2003), recall or selection bias; but, gene-environment interaction was proposed to be a major cause of the inconsistent observations (Baldacci et al 2015, Heinrich et al 2011).

Cockroaches exposure resulted a risk factor for wheeze, dry cough and severe AR, in line with many other studies (Baldacci et al 2015, Gold et al 2017). On the other hand, cockroaches exposure showed a negative association with asthma and eczema.

Carpets at home showed a negative association with asthma, wheeze, AR diagnosis and SPT positivity.

This negative association with cockroaches and carpets could be interpreted as efficacy of good practices to avoid exposure to risk factors in asthma/allergic children; indeed, one of the main medical recommendation in subjects with asthma/allergic diseases is to remove from house sources of allergens exposure like carpets (dust mites exposure) and cockroaches (Cipriani et al 2017, Gold et al 2017).

All the above reported results highlight the need to better understand susceptibility time windows to allergic sensitization and the dose-response relationships between allergen exposure, other heritable or environmental co-exposures (eg, stress and pollutants) and sensitization (Gold et al 2017).

The causal link between exposure to air pollutants and respiratory diseases is clearly reported in many international studies (Baldacci et al 2015, Maio et al 2016, WHO 2007, Thurston et al 2017). The exposure-response relationship is complex, depending on several factors, such as genetic susceptibility or gene-environment interaction (Jenerowicz et al 2012). Air pollutants exert their proinflammatory effects on airways by causing direct cellular injury or by inducing intracellular signaling pathways and transcription factors that are known to be sensitive to oxidative stress (D'Amato et al 2018).

The HEALS data showed that sources of air pollution near home and near school were significant risk factors for disease outcomes both in children and in general population sample. Living in home < 100m from main roads showed a positive association with asthma and severe asthma in general population sample and a negative association with eczema and SPT positivity in children sample.

Also the exposure to PM_{2.5} indoor/outdoor concentration level $\geq 25 \mu\text{g}/\text{m}^3$ showed controversial results in children sample: indoor PM_{2.5} showed a positive association with eczema and a negative association with asthma, wheeze and AR diagnosis; outdoor PM_{2.5} showed a positive association with asthma and wheeze and a negative association with dry cough and SPT positivity.

These contrasting results could be due to the presence of other risk factors not known in the HEALS database, to selection bias or to the interaction effect with other factors like the allergens exposure. The last aspect was taken into account in the "combined effect" analyses.

"Combined effect"

Allergic diseases are more common in highly developed countries suggesting that urban life promotes allergy. Indeed, airway mucosal damage and impaired mucociliary clearance induced by air pollution may facilitate access of inhaled allergens to the cells of the immune system, increasing the susceptibility to allergens (D'Amato et al 2018).

Four different statistical approaches were used to assess the possible effect of the combined exposure to allergens and air pollution on asthmatic and allergic diseases/symptoms: 1) interaction terms in the logistic regression analyses; 2) stratification of the logistic regression analyses by the 75th percentile of air pollutants concentration; 3) stratification of the logistic regression analyses by the levels of the "air pollutants cluster"; 4) logistic regression analyses using as independent variable the "combined exposure cluster".

First approach:

The first approach compared the effect of the exposure to only allergens or to only air pollutants with the exposure to both allergens and air pollutants.

The following combined exposures to allergens and air pollution increased the risk of disease outcomes with respect to the only exposure to allergens or to the only exposure to air pollution: mould and school outdoor PM_{2.5} $\geq 25 \mu\text{g}/\text{m}^3$ for having eczema; carpets and school outdoor PM_{2.5} $\geq 25 \mu\text{g}/\text{m}^3$ for wheeze; pets and school indoor PM_{2.5} $\geq 25 \mu\text{g}/\text{m}^3$ for asthma.

On the contrary, the following combined exposures to allergens and air pollution decreased the risk of disease outcomes with respect to the only exposure to allergens or to the only exposure to air pollution: pets and school indoor PM_{2.5} $\geq 25 \mu\text{g}/\text{m}^3$ for having AR symptoms; carpets and school indoor PM_{2.5} $\geq 25 \mu\text{g}/\text{m}^3$ for dry cough.

Second approach:

The second approach analyzed the effect of allergens exposure in subjects exposed to low concentration or high concentration of air pollutants.

Overall, exposure to at least one indoor allergen was a risk factor only in children exposed to low concentrations of air pollutants for dry cough, AR diagnosis and AR symptoms (OR ~ 1.24, 1.22, 1.12, respectively).

In particular, moulds exposure was a risk factor in children exposed to low O₃ concentration (OR 1.42 for wheeze, OR 1.88 for eczema and OR 1.55 for AR symptoms) and to high concentration of NO₂, and PM_{2.5} (OR 1.65 for AR symptoms and OR 2.42 for eczema, respectively). Likewise, cockroaches exposure showed: OR 2.14 for dry cough in children exposed to low O₃ concentration and OR of about 2.50 for dry cough, 2.71 for AR diagnosis and 3.24 for severe AR in children exposed to high NO₂ and PM concentration.

Overall, carpets exposure showed a negative association with asthma (OR ~ 0.36), wheeze (OR ~ 0.56), AR diagnosis (OR ~ 0.59) and SPT (OR ~ 0.62) in children exposed to low concentrations of air pollutants.

Finally, pets exposure showed contrasting results: it was a risk factor in children exposed to high concentrations of NO₂ for asthma (OR 2.07) and in those exposed to low concentrations of air pollutants for AR diagnosis (OR ~ 1.63). On the contrary, it showed a negative association with dry cough (OR ~ 0.52) and AR symptoms (OR ~ 0.69) in children exposed to low concentrations of air pollutants and with AR symptoms (OR 0.45) in those exposed to high concentrations of O₃.

Third approach:

The third approach analyzed the effect of allergens exposure in subjects exposed to different clusters of air pollutants exposure ("air pollutants cluster"). The third approach confirmed some of the results found using the second approach and it added no new information.

Fourth approach:

The fourth approach analyzed the effect of the combined exposure to allergens, air pollutants and asthma/allergic familiarity using the "combined exposure cluster".

The fourth approach confirmed the results found in the second approach regarding the exposure to at least one indoor allergen; in particular, the exposure to only allergens, with respect to the combined exposure to both allergens and air pollutants, was a risk factor for dry cough, AR diagnosis and AR symptoms.

Comparison between our results and those of other scientific researches was difficult because few studies about co-exposure to air pollutants and indoor allergens in general population were published, due to the difficulty to analyze this kind of association in uncontrolled settings (Baldacci et al 2015).

Indeed, our results lead in the same direction of a US study showing that prenatal exposure to cockroach allergens was associated with a larger risk of allergic sensitization (RR 1.15, 1.07-1.25); this risk was increased by exposure to nonvolatile PAHs (RR 1.22, 1.08-1.36) (Perzanowski et al 2013). In a study on a birth-cohort at high risk for asthma, co-exposure to dog allergen and NO₂ appears to increase the risk for asthma (OR 4.8, 1.1-21.5), as found in our data for pets exposure (Carlsten et al, 2011).

Moreover, our data suggested an interaction between moulds/cockroaches exposure and high concentration of NO₂, and PM_{2.5} as risk factor for allergic diseases. Combined exposure to pets and high concentrations of NO₂ was a risk factor for asthma in children while no influence of air pollution was evident for AR diagnosis. On the contrary, combined exposure to pets and high concentrations of O₃ was a protective factor for AR symptoms in children while no influence of air pollution was evident for dry cough and AR symptoms.

With regards to the "protective" effect found for carpets exposure, it might be interpreted as "selection bias" indicating efficacy of good practices to avoid exposure to risk factors in asthma/allergic children, like the removal of carpets from the houses of these children (Cipriani et al 2017). This effect remains effective in case of low air pollutants concentration, suggesting an antagonistic effect of exposure to high level of air pollutants.

Thus, our findings added new evidences about the effect of the interaction between air pollution and biological allergens on respiratory outcomes in real life setting. A confirmation may come from the comprehensive analyses that will be carried out in WP13 on EXHES data.

The clinical significance of this effect modification in the general population is uncertain (Baldacci et al 2015, Cakmak et al 2012) and possible explanations are primarily based on in vitro or animal studies (WHO 2013): ambient inhalable PM, because of their intrinsic electrostatic properties and porous surfaces, readily adhere to free airborne allergens released from animal dander, dust mites, moulds and pollens. PM may interact with aeroallergens, promoting airway sensitization by modulating the allergenicity of airborne allergens (Baldacci et al 2015, García Gallardo et al 2013, D'Amato et al 2002, D'Amato et al 2018). A recent clinical trial, using a comprehensive proteomic approach, demonstrated that inhaled diesel exhaust and allergen (mites and pollens) co-exposure could alter the allergen-mediated secreted global proteins in the human lung; this mechanism was not detected with mono-exposures (diesel exhaust or allergen alone) (Mookherjee et al 2018). The study identified new protein candidates enhanced by diesel exhaust and allergen co-exposure in humans; some of these proteins are inflammatory mediators and associated with uncontrolled asthma. Thus, atopic patients already sensitized to allergens may be more susceptible to following exposure to air pollution (Mookherjee et al 2018).

The importance of a better comprehension of the mechanisms underlying the effect of the combined exposure to pollution and allergens was recently stated during an international workshop, including in the research priorities: "Additional observational and animal model validation studies to assess the role of dose, route, timing, and pattern of single or multiple exposures, as well as genetic inheritance, in determining the relation of exposure to allergy or asthma development" (Gold et al 2017).

The following table reports the comparison of the main characteristics of the four statistical approaches used in our analyses to assess the combined exposure to allergens and air pollutants. The comparison suggested that the second approach (stratification of the logistic regression analyses by exposure to low or high concentration of air pollutants) is the most feasible and repeatable in other studies and easy to be interpreted, even if it doesn't permit to assess multiple exposures.

	Novelty	Feasibility	Easiness of results interpretation	Multiple exposure assessment	Repeatability in other studies
First approach	Low	High	Low	Yes	Yes
Second approach	Low	High	High	No	Yes
Third approach	High*	Medium*	High	Yes	No**
Fourth approach	High*	Medium*	Medium*	Yes	No**

* considering the use of the LCA analysis to compute the levels of the cluster

** clusters of exposure could be different in different population samples

LIMITS AND STRENGTHS OF THE HEALS PRE-EXISTING DATABASE

Limits: the most important limit of using pre-existing studies is that each of them has different main aims to be reached, different protocols and tools of data collection. In particular, this aspect

influenced the availability of comparable variables about the individual environmental exposure and thus, the possibility to perform statistical analysis on the HEALS harmonized database.

Moreover, there were less available data about biomarkers of health status, than expected, in the pre-existing databases.

Strengths: the main strength is the high sample size (about 27000 subjects) included the HEALS harmonized database and the possibility to replicate the same statistical analyses in different children subsample. Moreover, the health outcomes were available and comparable in all the selected pre-existing databases.

CONCLUSIONS AND RECOMMENDATIONS

WP14 findings will be taken into account for the statistical analyses to be performed in WP13 (“Exposure and health association studies”) aimed at analyzing WPs 14-17 data to synthesize the environment-wide associations between the exposure data and the observed biological effects/health outcomes in the populations studied in HEALS project (D13.2).

Moreover, the same statistical approaches of WP14 might be used in WP17 to compare the results found in the pre-existing studies (WP14) to those found in the harmonized EXHES-HEALS database from birth cohorts (WP17).

Data of the EXHES study will contain detailed questionnaires information about health and environmental exposure and results of omics- and epigenetic analyses performed on biological samples to assess the individual air pollution exposure during lifespan; the integration of such information about the individual exposure and effect will permit to refine the HEALS methodology for asthma/allergic diseases assessment presented in this deliverable. Thus, the limits about the use of pre-existing studies, with different protocols and data collection tools, will be overcome.

Moreover, one of the main aim of the HEALS project was to translate the learnt lessons during the project into scientific advice towards the development of protocols and guidelines for the setting up of a larger European environment and health examination survey.

The European HEALS database of children and general population pre-existing studies is a useful huge source of data.

The analyses described in this D14.2 permit to deliver the following recommendations useful to implement a European environment and health examination survey:

1) list of outcomes and environmental exposure data that should be taken into account in surveys focusing on asthma and allergic respiratory diseases:

General characteristics by Q	Disease outcomes by Q	Allergens exposure by Q	Environmental exposure by Q	Environmental exposure by instrumental measurements
Age	Childhood infections	Pets at home	Passive smoke	PM _{2.5} , PM ₁₀ , NO ₂ concentration within city (monitoring stations)
Gender	Asthma diagnosis	Cockroaches at home	Sources of air pollution near home	Indoor/outdoor PM _{2.5} concentration at school (short term campaigns)
Body mass index	Wheeze	Mould at home	Vehicular traffic near home	
Asthma/allergic disease familiarity	Dry cough	House dust mites	Sources of air pollution near school	

	Allergic disease diagnosis	Pollens*		
	Allergic disease symptoms			
	Eczema			

*arose from other scientific evidences

2) analyses on disease biomarkers didn't add further information with respect to the analyses performed on disease outcomes collected by questionnaire; thus, in large European environment and health examination surveys it is advisable to use easy and low-cost information collected through questionnaire in the general sample, reserving disease biomarkers for ad hoc selected sub-samples;

3) data on exposure to air pollution sources collected through questionnaire provide useful information about the subjects individual exposures;

4) short-term campaigns to measure the PM_{2.5} concentration near school would be useful, though with limited feasibility;

5) concentration data of air pollutants collected from monitoring stations at city level should be analyzed using new statistical methods permitting to obtain information at more finer spatial resolution, if data about individual exposure are not available; in particular, it would be useful to estimate the individual exposure at home address of the investigated subjects using GIS methodology. Methods to assess long-term exposure to outdoor air pollution have improved significantly over the past decade. Spatiotemporal models have been developed allowing more detailed temporal resolution compared to spatial models typically used for annual averages (Hoek et al 2017);

6) logistic regression models stratified by air pollutants concentration levels are feasible and useful statistical analyses to assess the effect of combined exposure to different risk factors and the same approach was used in other scientific researches (Cakmak et al 2012, Wang et al 2016). Latent class analysis might be used to describe the real pattern of combined exposure to different factors (i.e. allergens, air pollutants and diseases familiarity) in the investigated populations and to analyze the respiratory health effect, though less easy and repeatable than stratified analyses.

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Table 1. General characteristics of the European samples

Name	Country	Cities	Years	Cross – sectional or longitudinal study	Sample size	Age range	Sex
<i>Children samples</i>							
CCM	Italy	Pisa, Rome, Milan, Sondrio, Udine, Bari, Cagliari, Palermo	2010-2012	Cross- sectional	2573	6-15 yrs	51.0% M 49.0% F
REPRO_PL	Poland	Lodz and other Polish cities	2006-2015	Longitudinal	539	0-7 yrs	47.3% M 52.7% F
MAAS	UK	Manchester	1997-2014	Longitudinal	1184	1-17 yrs	54.2% M 45.8% F
EPITEEN	Portugal	Porto	2003-2004	Cross- sectional	2942	13 yrs	48.8% M 51.2% F
G21	Portugal	Porto	2005-2014	Longitudinal	8647	0-7 yrs	51.0% M 49.0% F
EDEN	France	Nancy, Poitiers	2003-2013	Longitudinal	2002	0-7 yrs	47.5% M 52.5% F
<i>General population samples</i>							
PISA1	Italy	Pisa	1985-1988	Cross- sectional	3865	4-97 yrs	47.6% M 52.4% F
PISA2	Italy	Pisa	1991-1993	Cross- sectional	2841	8-97 yrs	45.3% M 54.7% F
IMCA	Italy	Pisa	2009-2011	Cross- sectional	1620	18-103 yrs	47.3% M 52.7% F
SEASD	Italy	Pisa	1997-1998	Cross- sectional	639	13-99 yrs	0% M 100.0% F
CHIS2000	Spain	Barcelona and other Spanish cities	2001-2002	Cross- sectional	919	18-74 yrs	43.4% M 56.6% F

Table 2. Lifetime asthma and allergic symptoms/diseases (%)

	Asthma	Severe asthma# *	Wheeze	Dry cough	Eczem a	AR diagnosi s	Severe AR## *	AR symptoms
<i>Children samples</i>								
CCM	7.2	---	27.8	8.5	15.6	8.5	44.6	28.7
EDEN	25.2	18.8	44.1	---	42.2	82.1	78.6	35.9
G21	6.8	18.2	61.2	45.1	17.7	8.4	---	34.4
MAAS	39.5	52.8	28.2	---	42.0	28.8	---	40.9
REPRO_P L	10.4	--	1.5	6.4	21.1	1.9	---	9.9
EPITEEN	13.0	---	18.3	24.3	11.3	10.0	---	32.0
TOTAL	12.5	28.8	43.5	32.6	21.4	18.1	69.9	33.0
<i>General population samples</i>								
CHIS2000	4.2	---	---	---	7.0	16.8	--	---
IMCA	8.3	---	---	---	21.9	15.4	---	37.5
PISA1	6.9	---	18.5	15.1	---	16.4	---	---
PISA2	7.3	7.0	24.6	17.5	11.0	20.5	14.8	---
SEASD	7.4	---	10.7	11.9	9.1	22.6	---	---
TOTAL	7.0	7.0	20.2	15.7	13.1	17.8	14.8	37.5

AR: allergic rhinitis
 * computed only in subjects with
 asthma/AR diagnosis
 # computed by emergency department
 visits, hospitalizations, physician visits;
 ## computed by physician visits
 ## computed by impairment of daily
 activities

Table 3. Biomarkers of asthma and allergic diseases (%)

	AO	SPT	Blood eosinophilia	Dust/animals serum specific Ige	BHR
<i>Children samples</i>					
CCM	0.9	38.5	---	---	---
EDEN	0.1	---	16.9	15.9	---
G21	---	---	---	---	---
MAAS	2.7	28.0	---	8.4	18.4
REPRO_PL	0.0	31.6	---	---	---
EPITEEN	---	---	---	---	---
TOTAL	1.5	35.3	16.9	13.9	18.4
<i>General population samples</i>					
CHIS2000	---	---	---	---	---
IMCA	24.7	---	3.8	---	---
PISA1	---	----	---	---	---
PISA2	10.2	32.1	3.8	---	28.0
SEASD	---	---	2.2	---	---
TOTAL	14.1	32.1	3.5	---	28.0

AO: airway obstruction; SPT: skin prick test positivity; BHR: bronchial hyper-responsiveness

Table 4. Indoor/outdoor environmental exposure assessed by questionnaire (%)

	Passive smoke exposure	Mould exposure at home	Pets exposure at home	Cockroaches exposure at home	Carpets at home	Air pollution sources near home	Home distance ≤100m from road	Vehicular traffic near home	Air pollution sources near school	Work exposure
<i>Children samples</i>										
CCM	29.4	17.7	30.7	17.6	38.4	89.9	61.6	89.6	77.9	---
EDEN	71.0	---	63.8	13.3	---	---	---	---	---	---
G21	70.3	28.1	10.4	---	14.8	---	---	---	---	---
MAAS	14.8	---	---	---	---	---	---	---	---	---
REPRO_PL	36.5	15.5	6.3	1.9	41.6	16.5	---	---	---	---
EPITEEN	32.8	---	---	---	---	---	---	---	---	---
TOTAL	55.5	24.6	19.9	14.3	22.1	77.7	61.6	89.6	77.9	
<i>General population samples</i>										
CHIS2000	---	---	---	---	---	---	---	---	---	41.2
IMCA	22.9	---	53.0	---	---	---	---	65.9	---	44.1
PISA1	---	---	44.7	---	---	65.7	---	---	---	37.9
PISA2	51.4	---	48.0	---	---	56.5	28.4	39.3	---	41.9
SEASD	89.8	---	---	---	---	---	---	---	---	31.5
TOTAL	47.1		47.4			61.8	28.4	48.9		40.0

Table 5. Outdoor pollutants concentration measured by monitoring stations (EDMS HEALS database)

	O ₃ (study period mean)	O ₃ concentr ation > 75° perc*	NO ₂ (study period mean)	NO ₂ concentr ation > 75° perc*	NO ₂ concentr ation > 40 µg/m ³ (EU and WHO level) (%)	PM ₁₀ (study period mean)	PM ₁₀ concentr ation > 40 µg/m ³ (EU level) (%)	PM ₁₀ concent ration > 20 µg/m ³ (WHO level) (%)	PM ₁₀ concent ration > 75° perc*	PM _{2.5} (study period mean)	PM _{2.5} concent ration > 25 µg/m ³ (EU level) (%)	PM _{2.5} conce ntratio n > 10 µg/m ³ (WH O level) (%)	PM _{2.5} conce ntratio n > 75° perc*
<i>Children samples</i>													
CCM	40.58- 56.39* *	28.6	21.00- 119.71**	25.0	38.7	24.23- 42.68* *	0.0	100.0	25.0	17.00- 29.09**	32.7	100.0	33.3
EDEN	40.98- 44.44* *	0.0	48.4- 51.6**	0.0	0.0	21.85- 24.91* *	0.0	100.0	0.0	15.29- 16.07**	0.0	100.0	0.0
G21	34.75	0.0	48.27	0.0	100.0	32.89	0.0	100.0	0.0	---	---	---	---
MAAS	32.53	0.0	65.10	100.0	100.0	24.88	0.0	100.0	0.0	9.15	0.0	0.0	0.0
REPRO_P L	52.25	100.0	62.61	100.0	100.0	41.16	0.0	100.0	0.0	23.61	0.0	100.0	0.0
EPITEEN	33.58	0.0	44.48	0.0	100.0	43.36	0.0	100.0	100.0	---	---	---	---
TOTAL	39.18	23.1%	41.44	28.6%	80.0%	33.90	0.0%	100.0%	21.4%	16.90	10.8%	78.7 %	20.0 %
<i>General population samples</i>													
CHIS2000	28.62	0.0	54.92	0.0	100.0	48.46	0.0	100.0	100.0	---	---	---	---
IMCA	48.73	100.0	30.64	0.0	0.0	36.29	0.0	100.0	0.0	---	---	---	---
PISA1	---	---	---	---	---	---	---	---	---	---	---	---	---
PISA2	---	---	---	---	---	---	---	---	---	---	---	---	---
SEASD	---	---	---	---	---	---	---	---	---	---	---	---	---
TOTAL	41.45	50.0%	42.78	0.0%	36.2%	40.70	0.0%	100.0%	50.0%	---	---	---	---

*75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

** range of the mean concentration in cities involved in the study

Table 6. Indoor/outdoor pollutants concentration assessed by short term instrumental measurements

	Indoor PM _{2.5} concentration at school ≥25 µg/m ³	Indoor PM _{2.5} concentration at school ≥10 µg/m ³	Outdoor PM _{2.5} concentration at school ≥25 µg/m ³	Outdoor PM _{2.5} concentration at school ≥10 µg/m ³	Indoor PM ₁₀ concentration at school ≥20 µg/m ³	Outdoor PM _{2.5} concentration at home ≥25 µg/m ³	Outdoor PM _{2.5} concentration at home ≥10 µg/m ³	Dog allergens concentration in dust (classrooms) (>75°percentile: 13.33 ng/m ³)	Cats allergens concentration in dust (classrooms) (>75°percentile: 9.5 ng/m ³)	Mites allergens concentration in dust (classrooms) (>75°percentile: 2.03 ng/m ³)
<i>Children samples</i>										
CCM	58.6	95.4	37.6	90.1	---	---	---	25.3	25.3	25.0
EDEN	27.2	95.3	29.1	93.6	42.0	30.3	93.7	---	---	---
G21	---	---	---	---	---	---	---	---	---	---
MAAS	---	---	---	---	---	---	---	---	---	---
REPRO_P L	---	---	---	---	---	---	---	---	---	---
EPITEEN	---	---	---	---	---	---	---	---	---	---
TOTAL	48.1	95.4	34.1	91.5	42.0	30.3	93.7	25.3	25.3	25.0

STEP 1

CHILDREN SAMPLES

Table 7. Lifetime asthma and allergic symptoms/diseases by risk factors (%). The CCM study (n=2573) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe AR#° (n=433)	AO (n=1902)	SPT (n=1720)
Sex:									
males	9.2 ***	30.9 **	10.4 **	15.6	10.3 **	31.8 **	45.6	1.2	42.5 **
females	5.1	24.6	6.5	15.5	6.6	25.5	43.1	0.5	34.9
BMI:									
underweight	<i>6.3 b.l.</i>	26.6	7.8	16.1	7.8	27.3	42.1	0.8	35.1 **
normal	8.8	29.3	8.5	15.0	8.7	30.3	47.8	1.3	43.3
overweight/obese	5.8	30.1	11.9	12.1	10.9	33.7	46.2	0.0	42.3
Asthma/allergic rhinitis familiarity:									
no	4.2 ***	22.6 ***	6.8 **	13.0 ***	4.8 ***	21.4 ***	41.1	0.4 **	33.0 ***
yes	11.8	35.8	11.0	20.2	15.2	41.0	46.3	1.6	47.7
Childhood respiratory infections:									
no	3.1 ***	15.2 ***	6.0 ***	13.7 **	7.0 **	24.1 ***	39.7 *	1.1	35.9 **
yes	17.1	56.8	14.4	18.4	11.5	38.9	50.6	0.8	44.5
Mould exposure at home:									
no	6.9	26.3 **	7.4 ***	14.6 **	8.3	27.3 **	43.9	0.9	38.5
yes	8.6	32.9	13.7	20.7	10.3	34.5	46.2	1.0	39.2
Pets exposure at home:									
no	7.1	27.3	9.4 *	16.0	8.8	<i>29.8 b.l.</i>	44.8	<i>0.7 b.l.</i>	39.6
yes	7.4	28.3	6.2	15.2	8.2	26.2	43.1	<i>1.6</i>	36.2
Cockroaches exposure at home:									
no	7.1	27.0 *	7.6 ***	15.9	8.3	28.3	41.2 **	1.0	38.3
yes	8.0	33.3	13.2	15.1	9.7	32.2	57.5	0.6	39.9
Carpets at home:									
no	9.3 **	30.7 ***	8.6	16.4	9.7 **	30.3 *	43.3	0.7	41.8 **
yes	3.3	23.0	7.6	14.9	6.4	26.2	47.6	1.3	33.6
Passive smoke exposure:									
no	7.1	26.3 *	8.4	<i>16.5 b.l.</i>	8.5	27.9	43.6	1.0	38.2
yes	7.2	31.3	8.5	<i>13.3</i>	8.5	30.8	46.9	0.7	39.8
Air pollution sources near home:									
no	8.3	27.5	7.6	12.6	8.0	<i>23.6 b.l.</i>	36.1	1.2	35.6
yes	7.0	27.9	8.6	15.9	8.5	29.3	45.1	0.9	39.1

Home distance $\leq 100\text{m}$ from road:									
no	7.0	29.3	8.8	17.1	7.3	30.6	44.7	0.7	42.0
yes	7.9	28.5	9.1	14.5	9.1	31.3	48.3	1.0	39.2
Air pollution sources near school:									
no	5.4 *	23.0 *	10.1	15.9	6.0 *	27.8	38.8	1.9 *	<i>34.4 b.l.</i>
yes	8.1	28.7	7.8	14.6	9.5	29.9	44.3	0.6	<i>40.0</i>
Indoor PM _{2.5} concentration at school:									
<25 $\mu\text{g}/\text{m}^3$	7.5	27.2	8.4	12.0 **	7.3	30.5	45.9	1.1	40.2
$\geq 25 \mu\text{g}/\text{m}^3$	7.5	27.3	7.7	16.5	9.3	28.5	38.9	0.8	37.5
Outdoor PM _{2.5} concentration at school:									
<25 $\mu\text{g}/\text{m}^3$	6.3	<i>25.1 b.l.</i>	8.2 *	12.6 *	7.6	27.7	<i>50.0 b.l.</i>	0.5	39.4
$\geq 25 \mu\text{g}/\text{m}^3$	7.3	29.9	4.9	17.3	8.5	27.4	37.3	0.2	36.5
Dog allergens concentration in dust (classrooms) (75°perc):									
<13.33 ng/m^3	<i>8.0 b.l.</i>	28.2	17.4	16.8	9.5	28.8	43.4	1.2	37.8
$\geq 13.33 \text{ng}/\text{m}^3$	5.6	25.2	17.6	14.8	7.5	26.5	51.9	0.8	36.9
Cat allergens concentration in dust (classrooms) (75°perc):									
<9.5 ng/m^3	6.9	27.4	8.6	15.7	7.8	29.3	44.2	1.1	38.6
$\geq 9.5 \text{ng}/\text{m}^3$	8.1	28.4	7.6	14.6	9.8	26.2	44.9	0.6	39.4
Mites allergens concentration in dust (classrooms) (75°perc):									
<2.03 ng/m^3	8.0	29.3	8.2	17.1	9.4	28.7	41.3	0.8	36.8
$\geq 2.03 \text{ng}/\text{m}^3$	7.2	33.3	7.6	20.2	7.8	25.8	51.9	0.6	40.8

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis; AO: airway obstruction; SPT positivity: skin prick test

computed by impairment of daily activities; °computed only in subjects with asthma/AR diagnosis

Table 8. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The EPITEEN study (n=2942) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Sex:						
males	14.2	20.0 <i>b.l.</i>	22.0 *	11.5	11.7 *	32.8
females	11.9	16.9	26.3	11.1	8.5	31.3
BMI:						
underweight	13.4	17.9	24.3	11.4 <i>b.l.</i>	8.5	30.5
normal	13.0	18.6	24.3	10.3	10.6	32.5
overweight/obese	14.8	20.3	25.7	16.1	11.6	33.8
Asthma/allergic rhinitis familiarity:						
no	10.8 ***	15.2 ***	22.6 *	9.3 ***	7.0 ***	29.4 ***
yes	18.1	27.2	28.3	17.5	18.8	39.3
Passive smoke exposure:						
no	15.6	21.0	24.9	12.8	11.1	33.0
yes	16.1	24.3	29.8	14.4	10.4	36.6

p-value: * <0.05 ; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis

Table 9. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The EDEN study (n=2002) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#° (n=144)	Severe AR##° (n=1256)	Dust/animals serum specific IgE (n=684)	Blood eosinophilia (n=664)
Sex:										
males	23.8	43.8	n.a.	41.0	81.5	35.6	13.3	77.7	17.2	15.3
females	26.4	44.7		42.8	81.8	35.7	23.1	79.4	14.4	18.4
BMI:										
underweight	25.5	42.0	n.a.	41.6	82.1	36.6	16.2	79.4	16.4	16.8
normal	20.0	60.0		58.8	90.9	41.7	0.0	91.7	20.0	20.0
overweight/obese	---	---		---	---	---	---	---	---	---
Asthma/allergic rhinitis familiarity:										
no	24.2 <i>b.l.</i>	43.5	n.a.	41.1 <i>b.l.</i>	81.6	35.4	17.6	79.3	15.4	17.1
yes	28.5	45.9		45.8	83.4	37.6	22.2	76.4	18.0	16.2
Childhood respiratory infections:										
no	25.5	44.9	n.a.	41.9	81.3	35.6	18.3	78.7	15.5	16.8
yes	19.7	34.8		37.5	86.7	34.6	0.0	70.5	29.4	25.0
Pets exposure at home:										
no	27.2	45.0	n.a.	44.2	81.3	34.8	11.1	78.0	16.3	17.6
yes	23.0	42.6		40.7	83.8	33.3	22.5	80.4	13.5	14.8
Cockroaches exposure at home:										
no	25.5	44.1	n.a.	42.0	81.9	34.9	17.9	78.9	14.7 <i>b.l.</i>	16.8
yes	27.2	44.7		41.9	81.9	40.5	28.6	77.1	22.5	16.0
Passive smoke exposure:										
no	24.9	42.3	n.a.	41.6	82.7	39.1 <i>b.l.</i>	20.5	79.5	15.8	16.3
yes	25.4	45.2		42.4	81.5	34.2	17.5	78.3	15.8	17.1
Indoor PM _{2.5} concentration at school:										
<25 µg/m ³	24.0	40.6 <i>b.l.</i>	n.a.	43.1	80.7	35.3	15.3	79.5	17.1	17.3
≥25 µg/m ³	27.8	47.2		42.3	79.7	38.3	8.3	79.2	15.6	18.1
Outdoor PM _{2.5} concentration at school:										
<25 µg/m ³	24.0	40.1 *	n.a.	43.7	80.3	34.7	13.7	79.4	16.3	17.3
≥25 µg/m ³	28.1	47.1		43.3	79.4	39.4	10.3	79.4	17.7	17.1
Outdoor PM _{2.5} concentration at home:										
<25 µg/m ³	24.1	40.8	n.a.	43.7	79.7	36.8	13.2	80.3	16.7	18.0
≥25 µg/m ³	27.1	46.3		41.2	81.9	34.7	13.8	77.6	17.4	15.9
Indoor PM ₁₀ concentration at school:			n.a.							

<20 µg/m ³	21.9	40.9 *		39.8	80.0 *	32.8	18.2	76.9	17.1	14.3
≥20 µg/m ³	25.5	48.7		42.8	85.6	37.5	22.2	79.8	19.3	12.9

BMI: body mass index; AR: allergic rhinitis; p-value: * <0.05 ; b.l.: 0.1 > p-value >0.05 by chi-square test; # computed by emergency department visits, hospitalizations, physician visits; ## computed by physician visits; °computed only in subjects with asthma/AR diagnosis

Table 10. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The REPRO_PL study (n=539) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	SPT (n=98)
Sex:							
males	14.0	1.8	6.2	20.6	1.8	11.5	30.0
females	7.9	1.2	6.6	21.5	2.1	8.3	32.8
BMI:							
underweight	12.5	1.7	8.3	27.9	1.7	<i>15.0 b.l.</i>	25.0
normal	9.1	1.7	6.8	21.1	2.7	7.5	37.1
overweight/obese	14.3	0.9	4.4	17.7	0.0	<i>13.4</i>	15.0
Asthma/allergic rhinitis familiarity:							
no	9.3	1.5	6.3	19.8 *	1.2 *	8.7 *	24.1 ***
yes	20.0	1.0	7.1	30.4	5.2	15.6	71.4
Mould exposure at home:							
no	10.4	1.6	7.0	21.7	1.8	<i>8.9 b.l.</i>	33.3
yes	11.0	1.4	4.1	19.0	2.7	<i>15.3</i>	14.3
Pets exposure at home:							
no	0.0	0.9	6.5	20.6	1.5 ***	10.9	20.0
yes		0.0	0.0	34.8	13.6	17.4	---
Cockroaches exposure at home:							
no	6.6	1.5	6.4	22.1	2.0	10.1	31.6
yes	0.0	0.0	11.1	22.2	0.0	0.0	---
Carpets at home:							
no	<i>4.1 b.l.</i>	1.5	5.6	21.0	1.5	9.8	31.1
yes	<i>20.0</i>	1.1	7.4	24.1	2.6	10.0	30.0
Passive smoke exposure:							
no	10.9	1.0	5.9	20.1	2.0	10.2	36.2
yes	9.5	1.9	6.1	22.6	1.2	8.8	25.0
Air pollution sources near home:							
no	5.8	1.5	6.4	21.6	2.3	9.6	31.3
yes	11.1	1.3	6.5	24.7	0.0	11.7	33.3

p-value: * <0.05 ; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis; SPT: skin prick test positivity

Table 11. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The G21 study (n=8647) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#° (n=1949)
Sex:							
males	7.9 ***	64.8 ***	44.6	18.3	9.3 **	36.6 ***	20.1 *
females	5.6	57.5	45.6	17.1	7.5	32.1	16.2
BMI:							
underweight	<i>6.6 b.l.</i>	62.2 *	46.2	18.3	8.7	35.8	17.1 *
normal	<i>8.4</i>	66.1	48.0	18.4	9.6	33.3	24.0
overweight/obese	<i>2.3</i>	54.0	43.7	12.9	3.5	32.6	32.0
Asthma/allergic rhinitis familiarity:							
no	5.9 ***	60.0 ***	44.2 ***	17.2 ***	7.8 ***	33.1 ***	17.5
yes	14.7	70.9	52.3	23.0	14.2	44.5	20.5
Mould exposure at home:							
no	<i>6.7 b.l.</i>	61.2	44.8 ***	18.2	8.8 *	34.4 **	17.7
yes	<i>7.9</i>	63.4	50.6	19.9	11.0	38.2	18.1
Pets exposure at home:							
no	6.7	61.9	45.7	18.4 *	8.5	35.0	18.0
yes	6.8	60.7	47.1	15.0	9.3	33.7	16.3
Carpets at home:							
no	6.8	62.6	46.3	18.0	8.8	35.6	18.4
yes	6.2	62.1	45.9	19.2	7.9	34.6	16.3
Passive smoke exposure:							
no	6.4	58.1 ***	43.9	18.6	9.0	34.1	18.2
yes	6.9	62.9	46.0	17.5	8.2	34.9	17.9

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis

computed by impairment of daily activities; °computed only in subjects with asthma/AR diagnosis

Table 12. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The MAAS study (n=1184) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#° (n=916)	AO (n=982)	BHR (n=629)	Dust/animals serum specific IgE (n=249)
Sex:										
males	46.1***	32.3 **	n.a.	44.9 *	34.0 ***	44.9 **	62.0 ***	<i>3.6 b.l.</i>	22.6 **	<i>11.3 b.l.</i>
females	31.8	23.3		38.6	22.6	36.3	42.2	<i>1.8</i>	13.9	<i>5.2</i>
BMI:										
underweight	48.9 *	36.3	n.a.	41.6	37.0 **	46.7 **	62.2 *	2.2	28.6	5.6
normal	36.0	27.7		43.8	26.9	37.2	47.2	4.4	18.6	8.3
overweight/obese	44.0	35.6		43.3	42.2	53.8	55.3	2.2	15.9	11.1
Passive smoke exposure:										
no	37.9 *	26.5 **	n.a.	<i>43.0 b.l.</i>	28.2	40.1	51.9	2.5	18.4	9.2
yes	46.8	36.9		35.5	31.2	45.2	57.0	4.5	17.7	4.8

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

AO: airway obstruction; BHR: bronchial hyper-responsiveness; BMI: body mass index; AR: allergic rhinitis

computed by emergency department visits, hospitalizations, physician visits, °computed only in subjects with asthma/AR diagnosis

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Table 13. Lifetime asthma and allergic symptoms/diseases by risk factors (%). The PISA1 study (n=3865) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Sex:						
males	7.8 *	24.5 ***	20.4 ***	n.a.	15.9	n.a.
females	6.0	13.1	10.2		16.7	
BMI:						
underweight	8.1	13.7 ***	7.3 ***	n.a.	12.4 **	n.a.
normal	6.2	15.1	13.4		18.2	
overweight/obese	7.5	23.4	18.5		15.0	
Pets exposure at home:						
no	6.4	18.4	15.2	n.a.	15.6	n.a.
yes	7.5	18.6	14.8		17.3	
Air pollution sources near home:						
no	6.9	<i>16.9 b.l.</i>	<i>13.7 b.l.</i>	n.a.	13.4 ***	n.a.
yes	6.8	<i>19.3</i>	<i>15.8</i>		17.9	
Smoking habits:						
no smokers	6.4 **	10.8 ***	6.9 ***	n.a.	16.2	n.a.
ex-smokers	9.4	22.5	15.9		17.2	
smokers	6.0	31.0	30.8		16.1	
Work exposure:						
no	6.0 **	13.5 ***	10.3 ***	n.a.	15.2*	n.a.
yes	8.3	26.6	22.8		18.2	

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis

Table 14. Lifetime asthma and allergic symptoms/diseases by risk factors (%). The PISA2 study (n=2841) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#	Severe AR#°	AO (n=1890)	BHR (n=1158)	Blood eosinophilia (n=1919)	SPT (n=2184)
Sex:												
males	7.3	30.6 ***	21.7 ***	9.5 *	20.0	n.a.	7.0	14.3	14.2 ***	23.8 ***	5.1 **	16.0
females	7.2	19.6	14.0	12.3	20.9		7.1	15.3	6.2	33.3	2.5	16.1
BMI:												
underweight	10.2	17.6 ***	9.3 **	5.6	13.0 ***	n.a.	9.3	12.0 ***	1.6 ***	33.3	6.3	39.2 **
normal	6.9	21.2	16.1	10.9	24.4		6.8	18.2	7.8	26.1	4.1	35.2
overweight/obese	7.3	27.9	19.2	11.5	17.9		7.1	12.3	12.8	29.4	3.5	29.2
Smoking habits:												
no smokers	7.3	16.2 ***	10.2 ***	10.1	21.4	n.a.	7.0	15.6	5.1 ***	27.5	3.0	34.1
ex-smokers	8.1	27.5	16.9	12.2	19.7		7.9	15.1	13.1	26.8	4.6	30.6
smokers	6.1	39.1	33.6	11.6	19.5		6.1	12.8	15.4	30.1	4.3	30.5
Asthma/allergic rhinitis familiarity:												
no	6.4 ***	23.1 ***	17.3	<i>10.6 b.l.</i>	18.8 ***	n.a.	6.2 ***	13.5 ***	9.3 **	27.5	3.6	31.4 *
yes	12.6	34.2	19.3	<i>13.9</i>	31.8		12.3	24.1	16.0	31.4	5.0	36.9
Childhood respiratory infections:												
no	4.7 ***	21.1 ***	16.2 **	10.0 **	19.1 **	n.a.	4.6 ***	13.3 ***	8.1 ***	24.8 ***	4.1	31.6
yes	13.6	33.5	20.6	13.6	24.0		13.1	18.8	14.8	35.2	3.2	33.3
Pets exposure at home:												
no	7.0	24.1	17.7	11.5	20.5	n.a.	6.7	14.6	10.4	24.2 **	3.8	33.2
yes	7.5	25.2	17.3	10.4	20.4		7.4	15.0	10.0	31.5	3.8	31.1
Passive smoke exposure:												
no	7.3	25.1	17.0	<i>9.8 b.l.</i>	18.6 *	n.a.	7.1	<i>13.6 b.l.</i>	11.2	28.9	3.3	33.7
yes	7.1	24.1	18.0	<i>12.1</i>	22.3		6.9	<i>16.0</i>	9.3	27.4	4.2	30.9
Work exposure:												
no	7.6	20.6 ***	14.2 ***	10.6	20.2	n.a.	7.4	14.3	7.2 ***	27.6	3.6	32.1
yes	6.8	30.1	22.0	11.6	20.9		6.6	15.5	14.4	28.5	4.0	32.2
Air pollution sources near home:												
no	5.7 **	22.2 *	15.3 **	10.3	18.1 **	n.a.	5.5 **	12.4 **	9.1	27.0	3.3	31.3

yes	8.4	26.5	19.2	11.5	22.3		8.2	16.7	11.0	28.7	4.1	32.9
Vehicular traffic exposure near home:												
no	<i>6.3 b.l.</i>	<i>23.6 b.l.</i>	<i>16.4 b.l.</i>	10.4	20.1	n.a.	<i>6.1 b.l.</i>	13.5 *	<i>9.4 b.l.</i>	29.1	3.5	31.5
yes	8.2	26.4	19.0	11.3	21.1		8.0	16.3	11.9	25.6	4.6	34.3
Home distance ≤ 100 m from road:												
no	6.0 **	23.0 *	15.9	10.8	19.8	n.a.	5.9 **	14.5	9.5	27.7	3.8	32.4
yes	9.7	27.4	15.9	10.8	17.6		9.2	14.4	12.0	29.7	3.4	34.0

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05 by chi-square test

AO: airway obstruction; BHR: bronchial hyper-responsiveness; BMI: body mass index; AR: allergic rhinitis; SPT: skin prick test positivity

computed by physician visits; °computed only in subjects with asthma/AR diagnosis

Table 15. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The IMCA study (n=1620) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	AO (n=689)	Blood eosinophilia (n=692)
Sex:								
males	7.7	n.a.	n.a.	15.6 ***	14.9	37.4	30.4 **	3.9
females	8.9			27.4	15.9	37.6	19.6	3.6
BMI:								
underweight	0.0	n.a.	n.a.	50.5	0.0	0.0	0.0 ***	---
normal	10.6			25.6	17.7	38.6	11.1	4.0
overweight/obese	9.8			24.4	17.9	44.1	31.7	3.7
Smoking habits:								
no smokers	9.0	n.a.	n.a.	23.8	17.8*	37.5	17.0 ***	3.6
ex-smokers	8.6			20.7	12.7	39.9	34.6	3.8
smokers	6.6			19.3	14.4	34.0	24.8	4.0
Pets exposure at home:								
no	9.2	n.a.	n.a.	20.5	15.1	38.1	27.1	2.9
yes	7.6			23.1	15.7	37.1	22.0	4.7
Passive smoke exposure:								
no	7.8	n.a.	n.a.	21.1	15.7	36.7	26.1	3.3
yes	10.0			24.3	14.6	40.2	20.0	5.4
Work exposure:								
no	7.1 *	n.a.	n.a.	19.4 **	12.5 ***	33.0 ***	19.4 **	3.4
yes	9.9			24.9	19.2	43.3	29.9	4.1
Vehicular traffic near home:								
no	8.6	n.a.	n.a.	24.4	17.0	34.0 *	25.0	4.5
yes	8.6			21.5	15.3	40.3	24.2	3.4

p-value: * <0.05 ; *** <0.001 by chi-square test

BMI: body mass index; AR: allergic rhinitis; AO: airway obstruction

Table 16. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The SEASD study (n=639) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Blood eosinophilia (n=463)
Sex:							
males	---	---	---	---	---	n.a.	---
females	7.4	10.7	11.9	9.1	22.6		2.2
BMI:							
underweight	12.5	12.5	12.5	12.5	25.0	n.a.	0.0
normal	7.3	7.9	9.0	9.0	21.3		2.9
overweight/obese	7.2	10.8	15.1	8.6	24.7		1.4
Asthma/allergic rhinitis familiarity:							
no	5.4 ***	8.5 ***	10.1 **	7.6 **	21.5	n.a.	2.1
yes	16.8	20.4	20.5	16.8	27.4		2.4
Childhood respiratory infections:							
no	5.7 *	7.8 *	9.7	9.2	21.8	n.a.	2.0
yes	11.0	14.0	11.8	11.9	22.8		4.7
Passive smoke exposure:							
no	4.7	7.8	<i>4.7 b.l.</i>	10.9	29.7	n.a.	<i>5.9 b.l.</i>
yes	7.7	11.0	<i>12.7</i>	8.9	21.8		<i>1.7</i>
Work exposure:							
no	5.8 *	8.5*	10.8	7.5	21.3	n.a.	2.3
yes	11.4	15.2	15.3	10.9	26.6		1.5

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis

Table 17. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). The CHIS2000 study (n=919) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Sex:						
males	3.0	n.a.	n.a.	6.3	14.8	n.a.
females	5.2			7.5	18.3	
BMI:						
underweight	14.3 <i>b.l.</i>	n.a.	n.a.	9.5	33.3	n.a.
normal	3.5			5.9	16.2	
overweight/obese	4.4			7.6	16.5	
Smoking habits:						
no smokers	5.4	n.a.	n.a.	6.0	18.7	n.a.
ex-smokers	4.8			8.9	19.4	
smokers	2.3			7.3	13.3	
Work exposure:						
no	3.6	n.a.	n.a.	6.4	14.6 *	n.a.
yes	5.1			8.0	19.5	

p-value: * <0.05 ; b.l.: 0.1 > p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis

STEP 2

CHILDREN SAMPLES

Table 18. Lifetime asthmatic and allergic symptoms/diseases by risk factors (%). Cumulative analyses on children subsamples (n=17887) ("Independent effect")

	Asthma	Wheeze	Dry cough (n=14701) (except MAAS, EDEN)	Eczema	AR diagnosis	AR symptoms	Severe asthma#° (n=3009) (EDEN, G21, MAAS)	Severe AR##° (n=1689) (CCM, EDEN)	SPT (n=1818) (CCM, REPRO_PL)
Sex:									
males	10.4 **	52.2 ***	34.5	21.0	18.2	34.5 ***	32.9 ***	68.0	42.0 **
females	8.7	46.2	34.0	20.9	17.3	30.1	24.3	71.1	34.7
BMI:									
underweight	8.6	53.3 ***	38.4 ***	20.8 **	15.8 ***	34.2 ***	19.2 ***	68.5 ***	35.0 **
normal	8.8	37.3	21.8	17.8	8.5	27.4	39.6	50.9	42.7
overweight/obese	5.2	26.1	18.3	14.6	4.7	25.8	50.0	46.2	37.6
Asthma/allergic rhinitis familiarity:									
no	8.3 ***	49.3	35.5 ***	20.1 ***	16.8 ***	30.5 ***	17.5	73.4 ***	32.3 ***
yes	16.5	49.2	30.0	26.8	27.5	40.5	20.6	63.4	48.3
Childhood respiratory infections:									
no	<i>14.7 b.l.</i>	30.4 ***	48.9 ***	28.8 ***	44.0 ***	29.4 ***	---	71.9 ***	35.9 **
yes	<i>17.3</i>	54.8	51.1	19.9	18.0	38.6		54.8	44.5
Mould exposure at home:									
no	<i>6.8 b.l.</i>	47.7 ***	31.9 ***	17.4 **	8.3 **	30.8 ***	---	---	38.2
yes	8.8	55.6	42.2	20.0	10.6	36.8			38.6
Pets exposure at home:									
no	7.7 ***	50.9 ***	35.6 ***	19.1 ***	11.1 ***	<i>32.8 b.l.</i>	17.9	58.8 ***	39.6
yes	11.9	42.5	24.6	22.9	29.7	<i>30.4</i>	17.4	71.9	36.2
Cockroaches exposure at home:									
no	14.8	30.2 **	7.3 ***	26.2	33.7	28.0 **	---	69.1	38.0
yes	14.5	36.6	13.2	23.8	32.9	34.0		69.7	39.9
Carpets at home:									
no	7.3 ***	53.8 ***	37.2 ***	17.8	8.7 **	33.5 ***	---	---	41.3 **
yes	4.9	37.9	24.4	17.7	6.7	28.2			33.5

Passive smoke exposure:									
no	8.9 *	40.5 ***	26.0 ***	20.5	16.0***	30.6 **	37.3 ***	63.4 ***	38.1
yes	10.0	55.0	40.2	21.5	19.6	33.7	21.1	74.2	38.7
Air pollution sources near home:									
no	7.9	11.3 ***	6.9	18.3	4.4 **	14.7 ***	---	---	34.5
yes	7.1	26.9	8.5	16.2	8.2	28.6			39.0
Indoor PM _{2.5} concentration at school:									
<25 µg/m ³	15.0 **	33.3	8.4	26.5 **	39.2 ***	32.4	---	71.0 ***	---
≥25 µg/m ³	11.5	31.2	7.7	21.3	22.7	30.0		59.1	
Outdoor PM _{2.5} concentration at school:									
<25 µg/m ³	14.1	31.7 *	8.2 *	26.7	38.5 *	30.4	---	72.1	---
≥25 µg/m ³	14.9	36.2	4.9	26.2	33.3	31.2		68.4	

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05 by chi-square test

BMI: body mass index; AR: allergic rhinitis; SPT: skin prick test positivity

computed by physician visits, hospitalizations, emergency department visits, impairment of daily life, impairment of daily activities

computed by impairment of daily activities, physician visits

°computed only in subjects with asthma/AR diagnosis

GENERAL POPULATION SAMPLES

Table 19. Lifetime asthma and allergic symptoms/diseases by risk factors (%). Cumulative analyses on general population subsample (n=9844) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	AO (n=2579) (PISA2, IMCA)	Blood eosinophilia (n=3074) (PISA2, IMCA, SEASD)
Sex:								
males	7.7	27.0 ***	21.0 ***	10.9 ***	16.8 *	n.a.	18.3 ***	4.8 **
females	6.9	15.1	11.8	14.7	18.6		9.9	2.7
BMI:								
underweight	8.9 <i>b.l.</i>	14.6 ***	7.9 ***	7.2 *	13.7 ***	n.a.	1.6 ***	5.4
normal	6.5	17.0	14.2	11.9	20.0		8.6	3.9
overweight/obese	7.4	24.4	18.6	13.5	17.1		18.8	3.2
Smoking habits:								
no smokers	7.0 **	12.6 ***	8.8 ***	12.4 *	18.8 *	n.a.	8.3 ***	2.9 <i>b.l.</i>
ex-smokers	8.5	25.1	16.4	15.0	17.2		19.4	4.4
smokers	5.6	34.1	31.9	12.6	16.4		17.7	4.2
Asthma/allergic rhinitis familiarity:								
no	6.3 ***	20.6 ***	16.0 *	10.1 **	19.3 ***	n.a.	---	---
yes	13.6	31.0	19.5	14.6	30.8			
Childhood respiratory infections:								
no	4.9 ***	19.1 ***	15.2 **	9.9 **	19.5 **	n.a.	---	---
yes	13.2	30.7	19.3	13.4	23.8			
Pets exposure at home:								
no	7.1	20.7	16.2	14.6	17.2	n.a.	15.1	3.5
yes	7.5	21.5	15.9	15.3	18.0		13.0	4.0
Passive smoke exposure:								
no	7.5	24.4 **	16.5	15.1 *	17.5 **	n.a.	16.9 ***	3.4
yes	7.7	20.4	16.5	13.2	21.0		10.8	3.7
Work exposure:								
no	6.4 **	15.7 ***	11.8 **	11.9 **	16.6 ***	n.a.	10.1 ***	3.3
yes	8.0	27.3	22.0	14.9	19.7		19.1	3.7
Vehicular traffic near home:								
no	6.9 <i>b.l.</i>	23.6 <i>b.l.</i>	16.4 <i>b.l.</i>	13.8 *	19.4	n.a.	12.0 **	3.7
yes	8.4	26.4	19.0	16.2	18.3		16.6	4.1

AR: allergic rhinitis; AO: airway obstruction; p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test; n.a: not applicable.

STEP 3

CHILDREN SAMPLES

Table 20a. Lifetime asthma and allergic symptoms/diseases by air pollutants exposure (%). Analyses on children cumulative sample (n=17887) ("Independent effect")

	Asthma	Wheeze	Dry cough (n=14701) (except MAAS, EDEN)	Eczema	AR diagnosis	AR symptoms	Severe asthma#° (n=3009) (EDEN, G21, MAAS)	Severe AR##° (n=1689) (CCM, EDEN)	SPT (n=1818) (CCM, REPRO_PL)
O ₃ :									
≥ 75° perc. #	7.2***	14.1***	8.7***	16.6***	6.3***	22.1***	---	47.3***	36.5
< 75° perc.	12.9	46.5	36.1	22.2	19.3	34.1	28.8	72.9	37.3
NO ₂ :									
≥ 75° perc. #	26.8***	22.9***	7.6***	29.7***	17.8	31.8	52.8***	41.5***	36.5
< 75° perc.	10.2	47.6	35.5	19.8	18.1	33.2	18.3	72.6	39.0
PM ₁₀ :									
≥ 75° perc. #	12.0	19.6***	21.8***	12.3***	9.8***	31.7	---	49.3***	<i>33.0b.l.</i>
< 75° perc.	12.7	48.1	35.8	23.2	19.7	33.4	28.8	71.0	38.9
PM _{2.5} :									
≥ 75° perc. #	5.6***	<i>28.0b.l.</i>	9.1	19.4***	7.9***	26.8*	---	53.2***	33.0
< 75° perc.	24.3	<i>31.5</i>	7.6	33.3	40.8	32.0	48.2	73.2	37.0
Cluster:									
Only NO ₂ ≥ 75° perc. #	32.5***	28.6***	8.5***	35.3***	24.6***	39.1***	52.8***	33.3***	41.4
Only O ₃ ≥ 75° perc. #	10.0	51.8	38.2	21.8	19.5	32.7	18.3	74.0	36.6
PM ₁₀ & PM _{2.5} ≥ 75° perc. #	12.0	19.6	21.8	12.3	9.8	31.7	---	49.3	33.0

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05 by chi-square test

#75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

°computed only in subjects with asthma/AR diagnosis

Table 20b. Lifetime asthmatic and allergic symptoms/diseases by groups of exposure (clusters) (%). Analyses on children cumulative sample (n=13761) (except MAAS and EPITEEN) ("*Combined effect*")

	Cluster 1 (15.0%)	Cluster 2 (25.0%)	Cluster 3 (48.0%)	p-value
Asthma	10.0	8.0	6.6	0.017
Wheeze	54.9	18.0	26.5	<0.001
Dry cough	40.3	8.7	8.4	<0.001
Eczema	22.0	16.0	17.8	<0.001
AR diagnosis	20.1	7.5	8.9	<0.001
AR symptoms	33.6	24.9	30.3	<0.001

AR: allergic rhinitis; p-value by chi-square test

Cluster 1: subjects exposed to only allergens;

Cluster 2: subjects with asthmatic/allergic disease familiarity and exposed to allergens and high level of O₃ concentration ($\geq 75^{\circ}$ percentile);

Cluster 3: subjects with asthmatic/allergic disease familiarity and exposed to allergens and high levels of air pollutants concentration ($\geq 75^{\circ}$ percentile) (PM₁₀, PM_{2.5}, NO₂)

STEP 1

CHILDREN SAMPLES

Table 21a. Risk factors for lifetime asthma and allergic symptoms/diseases in the CCM study. Results of the logistic regression analyses (OR)

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe AR#°	SPT
Passive smoke exposure	0.60	1.24	1.03	0.71	1.13	0.94	1.07	0.83
Asthma/allergic rhinitis familiarity	5.96 ***	1.92 **	2.13 *	1.62 *	6.11 ***	2.06 ***	2.69 **	2.17 ***
Childhood respiratory infections	6.41 ***	7.55 ***	2.11 *	1.20	2.58 **	2.14 ***	0.92	1.27
Mould exposure at home	1.70	1.30	2.56 *	<i>1.69 b.l.</i>	1.63	1.68 *	0.78	1.02
Pets exposure at home	0.90	1.51	0.67	0.81	1.29	0.73	0.97	1.09
Cockroaches exposure at home	0.39 *	1.01	<i>1.77 b.l.</i>	<i>0.56 b.l.</i>	1.20	1.08	3.76 **	0.89
Carpets at home	0.39 *	0.61 *	0.83	0.80	0.89	1.28	1.28	0.80
Home distance ≤ 100 m from road	1.16	0.79	0.67	<i>0.67 b.l.</i>	1.04	0.88	1.08	0.66 *
Air pollution sources near school	<i>2.76 b.l.</i>	1.47	1.59	1.53	4.35 *	1.16	2.07	1.47
Indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	1.37	0.86	1.50	1.98 *	1.41	1.13	0.47	0.93
Outdoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.67	1.91 **	<i>0.54 b.l.</i>	1.12	1.13	0.93	0.95	0.62 *

("Independent effect")

AR: allergic rhinitis; SPT: skin prick test positivity

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; adjusted for sex, age and BMI

for spirometry: too few obstructed children to perform the logistic regression analyses
computed by impairment of daily activities; °computed only in subjects with asthma/AR diagnosis

Table 21b. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the CCM study. Results of the logistic regression analysis (OR) (interaction between allergens and air pollution exposure) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe AR#°	SPT
<i>Interaction between allergens and air pollution sources near school</i>								
Only mould exposure at home	1.46	1.19	3.12 **	0.95	0.63	0.94	0.30	0.68
Only pets exposure at home	1.30	0.77	0.57	0.77	0.89	0.51 *	0.37	1.26
Only cockroaches exposure at home	0.80	1.19	1.16	0.44	1.11	0.71	12.09 **	1.30
Only carpets at home	0.94	0.50 *	0.76	1.05	0.27 *	0.74	1.14	0.66
Only air pollution sources near school	<i>2.06 b.l.</i>	1.43	1.16	1.03	0.97	0.73	1.02	1.39
Mould exposure at home * air pollution sources near school	0.72	0.76	0.38 *	1.39	1.93	1.67	3.91	1.62
Pets exposure at home * air pollution sources near school	0.94	1.32	1.01	1.25	1.06	1.49	2.59	0.60
Cockroaches exposure at home * air pollution sources near school	0.79	0.85	1.30	1.79	0.91	1.70	0.12 *	0.69
Carpets at home * air pollution sources near school	<i>0.35 b.l.</i>	1.21	1.08	0.68	2.69	1.36	1.04	1.02
<i>Interaction between allergens and indoor PM_{2.5} concentration at school</i>								
Only mould exposure at home	0.88	0.90	1.24	1.34	0.84	1.35	0.69	1.32
Only pets exposure at home	0.62	1.00	0.57	1.06	1.22	0.55 **	1.12	0.87
Only cockroaches exposure at home	0.86	0.81	0.97	0.64	0.54	0.90	2.35	0.83
Only carpets at home	0.33 **	<i>0.68 b.l.</i>	1.30	<i>0.64 b.l.</i>	0.69	1.05	1.22	0.76
Only indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.67	1.07	1.08	1.35	1.07	0.83	0.69	0.99
Mould exposure at home * indoor PM _{2.5} concentration at school	1.65	1.08	1.52	0.86	1.52	1.04	1.92	<i>0.56 b.l.</i>
Pets exposure at home * indoor PM _{2.5} concentration at school	2.66 *	0.90	0.88	0.79	0.61	1.42	0.63	0.99
Cockroaches exposure at home * indoor PM _{2.5} concentration at school	0.79	1.57	2.14	1.16	2.40	1.41	0.95	1.25
Carpets at home * indoor PM _{2.5} concentration at school	1.37	0.78	0.41 *	1.36	0.91	0.87	1.01	0.79
<i>Interaction between allergens and outdoor PM_{2.5} concentration at school</i>								
Only mould exposure at home	1.44	0.70	2.17 *	0.93	1.23	1.27	0.65	0.80
Only pets exposure at home	0.73	0.93	0.70	0.98	0.61	0.61 *	0.94	1.03
Only cockroaches exposure at home	0.50	1.02	1.73	<i>0.53 b.l.</i>	0.85	1.23	3.25 *	1.05

Only carpets at home	0.24 **	0.47 **	0.44 *	0.86	<i>0.56 b.l.</i>	0.86	0.73	0.53 **
Only outdoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.51	0.93	0.63	1.10	0.51	0.72	<i>0.29 b.l.</i>	0.53 *
Mould exposure at home * outdoor PM _{2.5} concentration at school	1.20	1.92	0.92	2.55 *	0.69	1.45	2.59	1.04
Pets exposure at home * outdoor PM _{2.5} concentration at school	1.95	1.18	0.38	0.77	2.94 *	1.37	1.04	0.94
Cockroaches exposure at home * outdoor PM _{2.5} concentration at school	0.87	1.04	0.95	1.52	1.94	0.87	1.00	1.21
Carpets at home * outdoor PM _{2.5} concentration at school	4.06 *	2.17 *	3.79 *	0.81	1.26	1.56	<i>3.53 b.l.</i>	2.51 **

p-value: *
<0.05 ;

** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI, asthma/allergic rhinitis familiarity, childhood respiratory infections and passive smoke; # computed by impairment of daily activities; °computed only in subjects with asthma/AR diagnosis
AR: allergic rhinitis; SPT: skin prick test positivity; for spirometry: too few obstructed children to perform the logistic regression analyses

Table 22. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the EPITEEN study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Passive smoke exposure	1.03	1.19	1.27	1.19	0.97	1.09
Asthma/allergic rhinitis familiarity	1.31	1.28	1.35	1.93 **	2.37 ***	1.62 **

AR: allergic rhinitis. p-value: * <0.05 ; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex and BMI

Table 23a. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the EDEN study. Results of the logistic regression analysis (OR) (without interaction) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#°	Severe AR##°	Dust/animals specific IgE	Bloodeosinophilia
Passive smoke exposure	0.82	1.15	n.a.	0.94	0.89	0.70	---	0.78	2.84	0.84
Asthma/allergic rhinitis familiarity	1.07	0.74	n.a.	<i>1.52 b.l.</i>	1.28	1.06	---	0.97	1.28	1.25
Childhood respiratory infections	2.29	1.30	n.a.	0.42	3.23	0.63	---	1.11	---	---
Pets exposure at home	1.00	1.05	n.a.	1.38	1.45	0.73	---	0.99	1.05	0.91
Cockroaches exposure at home	0.92	1.34	n.a.	1.24	0.98	1.74	---	0.58	2.76	1.30
Indoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	1.49	1.05	n.a.	0.82	1.03	1.45	---	0.96	0.87	1.15
Outdoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	<i>1.68 b.l.</i>	1.38	n.a.	0.99	0.81	1.68	---	1.27	1.70	1.96

Outdoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at home	0.75	0.92	n.a.	1.26	1.24	0.53	---	0.85	1.04	0.67
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AR: allergic rhinitis; p-value: * <0.05 ; b.l.: $0.1 > \text{p-value} > 0.05$; Adjusted for sex; # computed by emergency department visits, hospitalizations, physician visits; ## computed by physician visits; °computed only in subjects with asthma/AR diagnosis

Table 23b. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the EDEN study. Results of the logistic regression analysis (OR) (interaction between allergens and air pollution exposure) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#°	Severe AR##°	Dust/animals specific IgE	Bloodeosinophilia
<i>Interaction between allergens and indoor PM_{2.5} concentration at school</i>										
Only pets exposure at home	0.93	1.19	n.a.	1.02	1.51	0.59 b.l.	---	1.10	1.28	0.66
Only cockroaches exposure at home	1.19	1.23	n.a.	0.98	1.05	3.26 **	---	0.58	4.85 *	2.58
Only indoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	1.42	1.19	n.a.	0.53 b.l.	1.04	0.92	---	1.02	2.72	0.32
Pets exposure at home * indoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	1.25	0.79	n.a.	2.44 b.l.	1.26	2.64 b.l.	---	0.78	---	8.11
Cockroaches exposure at home * indoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	0.72	1.18	n.a.	2.21	0.6	0.20 *	---	1.05	0.31	1.12
<i>Interaction between allergens and outdoor PM_{2.5} concentration at school</i>										
Only pets exposure at home	1.07	1.00	n.a.	1.16	1.61	0.70	---	0.90	1.09	0.65
Only cockroaches exposure at home	0.67	1.05	n.a.	1.12	0.92	2.12 b.l.	---	0.69	3.27	1.59
Only outdoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	1.67	1.05	n.a.	0.69	1.00	1.35	---	0.94	1.98	1.13
Pets exposure at home * outdoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	0.79	1.25	n.a.	1.90	0.80	1.17	---	1.92	0.96	2.64
Cockroaches exposure at home * outdoor PM _{2.5} concentration ≥ 25 $\mu\text{g}/\text{m}^3$ at school	2.14	2.00	n.a.	1.43	1.25	0.58	---	0.52	0.66	0.63
<i>Interaction between allergens and outdoor PM_{2.5} concentration at home</i>										
Only pets exposure at home	0.95	1.15	n.a.	1.13	1.58	0.56 *	---	0.80	0.86	0.61

Only cockroaches exposure at home	1.03	1.56	n.a.	0.96	1.02	2.65 *	---	0.69	6.81 **	3.87 *
Only outdoor PM _{2.5} concentration $\geq 25 \mu\text{g}/\text{m}^3$ at home	1.23	1.27	n.a.	0.82	1.05	0.57	---	0.56	3.25	---
Pets exposure at home * outdoor PM _{2.5} concentration $\geq 25 \mu\text{g}/\text{m}^3$ at home	1.00	0.89	n.a.	1.52	1.05	3.14 *	---	2.89	0.55	---
Cockroaches exposure at home * outdoor PM _{2.5} concentration $\geq 25 \mu\text{g}/\text{m}^3$ at home	1.19	0.53	n.a.	2.04	0.70	0.38	---	0.56	0.11	---

AR: allergic rhinitis; # computed by emergency department visits, hospitalizations, physician visits; ## computed by physician visits; °computed only in subjects with asthma/AR diagnosis

p-value: * <0.05 ; b.l.: 0.1 > p-value >0.05; Adjusted for sex, passive smoke, asthma/allergic rhinitis familiarity and childhood respiratory infections

Table 24a. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the REPRO_PL study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Passive smoke exposure	---	---	1.04	1.14	---	1.14
Asthma/allergic rhinitis familiarity	---	---	0.76	<i>1.74 b.l.</i>	---	<i>1.97 b.l.</i>
Mould exposure at home	---	---	0.49	0.71	---	1.48
Pets exposure at home	---	---	---	2.04	---	1.57
Cockroaches exposure at home	---	---	1.82	1.35	---	---
Carpets at home	---	---	1.83	1.16	---	0.94
Air pollution sources near home	---	---	1.04	<i>1.91 b.l.</i>	---	0.89

AR: allergic rhinitis

p-value: * <0.05 ; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex and BMI

Table 24b. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the REPRO_PL study. Results of the logistic regression analysis (OR) (interaction between allergens and air pollution exposure) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
<i>Interaction between allergens and air pollution sources near home</i>						
Only mould exposure at home	---	---	0.33	0.60	---	1.41
Only pets exposure at home	---	---	---	1.38	---	2.03
Only cockroaches exposure at home	---	---	1.85	1.31	---	---
Only carpets at home	---	---	1.87	1.13	---	1.01
Only air pollution sources near home	---	---	0.91	1.09	---	1.25
Mould exposure at home* air pollution sources near home	---	---	3.32	1.94	---	1.17
Pets exposure at home* air pollution sources near home	---	---	1.54	---	---	---
Cockroaches exposure at home* air pollution sources near home	---	---	---	---	---	---
Carpets exposure at home* air pollution sources near home	---	---	0.84	1.43	---	0.60

AR: allergic rhinitis

p-value: * <0.05 ; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex and BMI

Table 25. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the G21 study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#°
Passive smoke exposure	1.09	1.23 **	1.17 *	0.94	0.97	1.06	0.95
Asthma/allergic rhinitis familiarity	2.86 ***	1.54 ***	1.40 ***	1.32 *	1.74 ***	1.51 ***	1.26
Mould exposure at home	1.18	<i>1.13 b.l.</i>	1.25 **	1.26 **	<i>1.23 b.l.</i>	1.19 *	1.16
Pets exposure at home	1.10	0.94	1.03	0.85	1.13	0.93	0.99
Carpets at home	1.00	0.93	0.88	1.01	0.89	0.90	0.77

AR: allergic rhinitis; # computed by emergency department visits, hospitalizations, physician visits; °computed only in subjects with asthma/AR diagnosis

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex and BMI

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Table 26. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the PISA1 study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Pets exposure at home	1.20	1.04	1.04	n.a.	1.11	n.a.
Air pollution sources near home	1.04	1.29 **	1.30 *	n.a.	1.36 **	n.a.
Work exposure	1.42 *	1.50 ***	1.49 **	n.a.	1.34 **	n.a.

AR: allergic rhinitis

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for BMI, age, sex, educational level, work position and smoking habits

Table 27. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the PISA2 study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe asthma#°	Severe AR##°	AO	BHR	Blood eosinophilia	SPT
Passive smoke exposure	1.09	0.87	1.22	1.16	<i>1.25 b.l.</i>	n.a.	1.13	1.15	1.11	1.06	<i>1.90 b.l.</i>	0.66 ***
Asthma/allergic rhinitis familiarity	2.30 ***	1.69 **	0.98	1.56 *	1.87 ***	n.a.	2.29 ***	1.88 ***	2.58 ***	1.09	1.66	<i>1.31 b.l.</i>
Childhood respiratory infections	2.95 ***	1.87 ***	1.57 **	<i>1.34 b.l.</i>	1.39 **	n.a.	2.88 ***	1.52 **	2.07 ***	1.73 **	0.71	1.10
Pets exposure at home	1.12	1.18	1.13	0.83	1.03	n.a.	1.14	1.04	0.95	1.22	0.93	0.92
Air pollution sources near home	1.36	1.10	1.04	1.15	1.17	n.a.	1.35	1.32 *	0.89	0.96	1.04	<i>1.22 b.l.</i>
Home distance ≤100m from road	1.54 *	1.19	0.92	0.96	0.81	n.a.	1.51 *	0.92	1.13	1.08	0.92	1.04
Work exposure	0.77	1.05	0.99	<i>1.37 b.l.</i>	1.14	n.a.	0.77	1.28	0.89	1.00	1.11	1.18

BHR: bronchial hyper-responsiveness; BMI: body mass index; AR: allergic rhinitis; AO: airway obstruction; SPT: skin prick test positivity

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for BMI, age, sex, educational level, work position and smoking habits

computed by emergency department visits, hospitalizations, physician visits; ## computed by physician visits; °computed only in subjects with asthma/AR diagnosis

Table 28. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the IMCA study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	AO	Blood eosinophilia
Passive smoke exposure	1.26	n.a.	n.a.	1.32	0.98	1.44 *	0.84	1.75
Pets exposure at home	0.89	n.a.	n.a.	1.13	1.13	0.93	0.97	1.25
Vehicular traffic near home	0.97	n.a.	n.a.	0.85	0.94	1.17	0.60 *	0.84
Work exposure	1.30	n.a.	n.a.	1.64 **	1.87 **	1.39 *	1.42	1.57

AR: allergic rhinitis; AO: airway obstruction

p-value: * <0.05 ; *** <0.001; Adjusted for BMI, age, sex, educational level and smoking habits

Table 29. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the SEASD study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Blood eosinophilia
Passive smoke exposure	0.69	0.58	1.05	0.43	0.56	n.a.	0.84
Asthma/allergic rhinitis familiarity	7.23 ***	4.83***	3.24 **	3.64 **	1.47	n.a.	0.72
Childhood respiratory infections	3.19 *	3.30 **	1.59	0.85	1.06	n.a.	2.62
Work exposure	1.95	1.95	1.68	1.14	1.03	n.a.	1.00

AR: allergic rhinitis

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for BMI, sex, and age

Table 30. Risk factors for lifetime asthmatic and allergic symptoms/diseases in the CHIS2000 study. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Work exposure	1.62	n.a.	n.a.	1.35	1.54 *	n.a.

AR: allergic rhinitis

p-value: * <0.05 ; b.l.: 0.1 > p-value >0.05; Adjusted for BMI, sex, age and smoking habits

STEP 2

CHILDREN SAMPLES

Table 31a. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	SPT
Passive smoke exposure	0.99	1.40*	1.14	0.85	1.08	1.26*	1.10
Asthma/allergic rhinitis familiarity	3.36 ***	1.97 ***	1.76 **	1.74***	4.19 ***	2.64 ***	2.09 ***
Mould exposure at home	1.22	1.20	<i>1.4 b.l.</i>	1.19	1.16	1.39 *	1.01
Pets exposure at home	1.16	1.00	0.57 **	0.99	1.01	0.73**	0.83
Cockroaches exposure at home	0.85	1.15	1.54 *	0.89	1.11	1.05	0.95
Carpets at home	0.37 ***	0.64 ***	0.95	0.83	0.65 *	0.94	0.68 **
Air pollution sources near home	0.79	0.95	1.10	<i>1.44b.l.</i>	0.85	1.03	1.00

AR: allergic rhinitis; SPT: skin prick test positivity

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI, study attendance

Table 31b. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	SPT
Passive smoke exposure	0.98	1.44*	1.28	0.84	0.78	1.33*	1.06
Asthma/allergic rhinitis familiarity	3.69***	1.96***	1.34	1.65**	3.94***	2.50***	2.07***
Mould exposure at home	1.11	1.14	1.12	0.96	1.07	1.31	1.02
Pets exposure at home	1.44	1.15	0.51**	0.79	0.98	0.80	0.79
Cockroaches exposure at home	0.81	1.30	2.33**	0.98	1.34	1.17	0.84
Carpets at home	0.41**	0.61**	1.10	<i>0.78b.l.</i>	0.70	1.05	0.70*
Air pollution sources near home	0.80	1.36	1.10	1.47	0.79	1.13	1.01
O ₃ ≥ 75° perc. #	0.73	0.34***	1.05	0.89	1.07	1.01	0.88
NO ₂ ≥ 75° perc. #	0.91	0.55***	0.96	0.87	1.05	1.42*	1.04
PM ₁₀ ≥ 75° perc. #	---	---	---	---	---	---	---
PM _{2.5} ≥ 75° perc. #	0.66	0.95	1.02	0.95	0.90	0.81	0.76

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI

Table 31c. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	SPT
Passive smoke exposure	0.97	1.54**	1.23	0.88	0.92	1.36*	1.14
Asthma/allergic rhinitis familiarity	3.55***	1.97***	1.69**	1.66***	4.48***	2.78***	2.22***
Mould exposure at home	1.19	1.10	1.19	1.06	1.08	1.34*	1.01
Pets exposure at home	1.32	1.01	0.57*	0.88	0.93	0.72*	<i>0.77b.l.</i>
Cockroaches exposure at home	0.82	1.18	2.11**	0.95	1.37	1.19	0.85
Carpets at home	0.41***	0.62***	1.00	0.80	<i>0.71b.l.</i>	0.98	0.71*
Air pollution sources near home	0.82	0.87	1.27	1.41	0.90	1.04	0.97
Cluster: Only NO ₂ ≥ 75° perc. # PM ₁₀ & PM _{2.5} ≥ 75° perc. # (ref. only O ₃ ≥ 75° perc. #)	1.06 0.69	0.93 0.82	1.01 0.92	0.97 1.02	0.94 0.83	1.26 0.98	1.04 0.79

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 31d. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) (interaction between allergens and air pollution sources near home) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	SPT
Only mould exposure at home	1.28	1.79	0.43	0.69	0.46	1.63	0.66
Only pets exposure at home	1.13	0.69	0.45	1.11	1.79	0.87	1.01
Only cockroaches exposure at home	---	0.45	2.88	1.26	---	0.39	1.36
Only carpets at home	0.45	0.81	1.05	0.62	0.96	0.84	<i>0.49 b.l.</i>
Only air pollution sources near home	0.74	0.59	0.95	1.21	0.93	0.97	0.89
Mould exposure at home * air pollution sources near home	0.96	0.64	<i>3.88 b.l.</i>	1.90	2.75	0.83	1.42
Pets exposure at home * air pollution sources near home	1.03	1.49	1.28	0.88	0.52	0.82	0.80
Cockroaches exposure at home * air pollution sources near home	---	2.71	0.50	0.68	---	2.86	0.68
Carpets exposure at home * air pollution sources near home	0.80	0.78	0.89	1.41	0.64	1.15	1.44

AR: allergic rhinitis; SPT: skin prick test positivity

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, BMI, age, passive smoke, asthma/allergic rhinitis familiarity, study attendance

Table 31e1. Risk factors for lifetime asthma symptoms/diagnosis stratified by air pollutants concentration. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Asthma		Wheeze		Dry cough	
		< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#
Asthma/allergic rhinitis familiarity	O ₃	3.48***	3.27**	1.81***	2.23***	1.60*	2.05*
	NO ₂	3.18***	4.06***	1.77***	2.59***	2.14***	1.37
	PM ₁₀	3.06***	10.89**	2.01***	2.57**	1.71**	1.89
	PM _{2.5}	3.13***	5.48**	1.80***	2.01**	1.21	<i>1.97b.l.</i>
Passive smoke exposure	O ₃	1.09	1.07	<i>1.32b.l.</i>	2.28***	1.08	1.37
	NO ₂	0.97	1.05	1.39*	<i>1.47b.l.</i>	1.17	1.05
	PM ₁₀	0.93	0.64	<i>1.29b.l.</i>	2.13*	1.19	0.95
	PM _{2.5}	1.05	1.11	1.29	1.67*	1.31	0.79
Mould exposure at home	O ₃	1.58	0.93	1.42*	0.88	1.39	1.08
	NO ₂	1.27	1.15	1.26	1.00	1.86**	0.89
	PM ₁₀	1.13	1.72	1.27	0.63	1.37	1.88
	PM _{2.5}	1.04	1.97	1.28	1.05	1.00	1.82
Pets exposure at home	O ₃	1.25	1.23	1.10	0.74	0.50*	<i>0.54b.l.</i>
	NO ₂	0.96	1.59	0.96	0.97	0.55*	0.63
	PM ₁₀	1.13	2.05	0.99	0.96	0.59*	0.91
	PM _{2.5}	1.35	1.47	1.16	0.96	0.44**	0.60
Cockroaches exposure at home	O ₃	0.77	1.03	1.14	1.29	2.14**	2.01
	NO ₂	0.88	0.78	1.20	1.19	1.13	2.44**
	PM ₁₀	1.00	<i>0.10b.l.</i>	1.19	0.89	1.35	2.80*
	PM _{2.5}	1.19	0.50	1.36	1.15	2.32*	2.27*
Carpets at home	O ₃	0.43**	0.35*	0.84	0.38***	1.18	0.73
	NO ₂	0.35***	0.39*	0.60***	0.78	0.95	1.01
	PM ₁₀	0.32***	0.79	0.54***	1.05	0.92	1.20
	PM _{2.5}	0.34***	0.54	0.53***	1.09	1.07	1.10
Air pollution sources near home	O ₃	0.59	1.21	0.97	1.30	1.48	1.30
	NO ₂	0.85	0.65	0.86	5.37**	1.62	0.75
	PM ₁₀	0.74	---	1.22	---	1.25	---
	PM _{2.5}	0.76	---	<i>1.54b.l.</i>	2.15	1.15	---

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 31e2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants concentration. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Eczema		AR diagnosis		AR symptoms		SPT	
		< 75° perc.#	≥75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#
Asthma/allergic rhinitis familiarity	O ₃	1.52*	1.95**	4.64***	4.26***	2.57***	3.50***	1.98***	2.88***
	NO ₂	1.64**	1.96**	4.09***	4.77***	2.94***	2.23***	2.33***	1.85**
	PM ₁₀	1.78***	1.49	4.17***	4.89**	2.84***	1.88*	2.21***	1.70
	PM _{2.5}	1.70**	<i>1.64b.l.</i>	3.66***	4.10***	2.78***	1.98**	2.31***	1.70
Passive smoke exposure	O ₃	<i>0.71b.l.</i>	1.05	0.88	1.20	1.39*	1.38	0.90	1.65*
	NO ₂	0.96	0.73	1.45	0.62	1.12	1.46*	1.15	0.95
	PM ₁₀	0.97	0.38*	1.23	<i>0.24b.l.</i>	1.23	1.47	1.10	0.97
	PM _{2.5}	0.94	0.48*	0.95	0.58	<i>1.32b.l.</i>	1.23	1.05	0.97
Mould exposure at home	O ₃	1.88**	<i>0.59b.l.</i>	1.30	0.89	1.55*	1.05	1.23	0.83
	NO ₂	1.21	1.13	1.21	1.09	<i>1.31b.l.</i>	1.65*	0.83	<i>1.79b.l.</i>
	PM ₁₀	0.96	1.97	1.25	0.72	1.39*	1.25	0.94	1.66
	PM _{2.5}	0.83	2.42**	1.24	0.99	1.23	1.33	0.89	1.66
Pets exposure at home	O ₃	0.83	1.26	1.11	0.83	0.85	0.45**	0.85	<i>0.64b.l.</i>
	NO ₂	1.01	0.94	0.96	1.10	0.63**	0.98	0.86	0.76
	PM ₁₀	0.96	0.77	1.01	0.76	0.75*	0.66	0.85	0.71
	PM _{2.5}	0.82	1.08	1.02	1.11	0.80	0.67	0.79	0.71
Cockroaches exposure at home	O ₃	1.10	0.90	<i>1.63b.l.</i>	0.84	1.27	0.97	0.89	0.69
	NO ₂	0.84	1.02	0.83	<i>1.89b.l.</i>	0.96	1.19	0.87	1.10
	PM ₁₀	<i>0.66b.l.</i>	0.97	0.83	2.88*	0.98	1.36	0.92	1.24
	PM _{2.5}	0.90	1.15	0.98	2.53*	1.10	1.46	0.72	1.24
Carpets at home	O ₃	0.91	0.75	0.60*	0.70	0.97	0.91	0.85	0.52**
	NO ₂	0.81	0.84	0.57*	0.86	0.89	1.12	0.60***	0.81
	PM ₁₀	0.80	0.83	<i>0.70b.l.</i>	0.73	0.87	<i>1.70b.l.</i>	0.63***	1.08
	PM _{2.5}	0.77	0.94	0.70	<i>0.45b.l.</i>	0.89	1.34	0.62**	1.08
Air pollution sources near home	O ₃	1.43	1.39	1.00	0.96	1.20	1.08	0.66	1.23
	NO ₂	1.19	<i>1.72b.l.</i>	0.89	0.93	1.11	1.01	1.18	0.59
	PM ₁₀	1.26	1.59	0.85	---	1.09	1.78	1.09	0.28
	PM _{2.5}	<i>1.57b.l.</i>	0.99	0.72	---	1.09	3.15	1.11	0.28

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI

Table 31f1. Risk factors for lifetime asthmatic symptoms/diseases stratified by air pollutants cluster. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Asthma			Wheeze			Dry cough		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	2.34*	3.43***	10.89**	2.65***	1.66**	2.57**	1.35	1.78*	1.89
Passive smoke exposure	1.15	0.98	0.64	1.05	1.70**	2.13*	0.81	1.42	0.95
Mould exposure at home	0.83	1.22	1.72	1.52	1.14	0.63	0.42	1.22	1.88
Pets exposure at home	1.56	1.08	2.05	0.98	0.97	0.96	0.49	0.50*	0.91
Cockroaches exposure at home	1.91	0.79	<i>0.10b.l.</i>	1.48	1.23	0.89	<i>2.63b.l.</i>	1.87	2.80*
Carpets at home	0.09*	0.42**	0.79	<i>0.55b.l.</i>	0.57***	1.05	0.54	1.06	1.20
Air pollution sources near home	0.36	0.85	---	1.65	1.08	---	<i>0.25b.l.</i>	1.48	---

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 31f2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants cluster. Cumulative analyses on CCM and REPRO_PL subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Eczema			AR diagnosis			AR symptoms			SPT		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	2.60**	1.55*	1.49	5.58***	4.19***	4.89**	2.88***	3.21***	1.88*	1.98*	2.72***	1.70
Passive smoke exposure	0.78	1.06	0.38*	0.82	1.25	<i>0.24b.l.</i>	1.51	1.26	1.47	0.88	1.25	0.97
Mould exposure at home	1.39	0.88	1.97	2.02	1.03	0.72	<i>1.94b.l.</i>	1.21	1.25	2.01	0.81	1.66
Pets exposure at home	0.89	0.92	0.77	0.94	0.91	0.76	1.42	0.58**	0.66	0.78	<i>0.74b.l.</i>	0.71
Cockroaches exposure at home	0.95	0.86	0.97	1.86	0.78	2.88*	1.08	1.03	1.36	1.14	<i>0.55b.l.</i>	1.24
Carpets at home	1.07	0.76	0.83	0.90	0.68	0.73	0.78	0.89	<i>1.70b.l.</i>	0.69	0.63**	1.08
Air pollution sources near home	3.29	1.42	1.59	0.78	0.84	---	0.58	1.06	1.78	0.54	1.09	0.28

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 32a. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe AR#°
Passive smoke exposure	0.74	1.21 **	---	0.88	0.96	0.99	1.43
Asthma/allergic rhinitis familiarity	3.17 ***	1.56 **	---	1.57 **	4.82**	2.02 ***	1.41
Childhood respiratory infections	5.15 ***	6.59 ***	---	1.29	1.77*	1.70 ***	0.91
Pets exposure at home	0.93	0.96	---	0.94	1.13	0.68 *	1.11
Cockroaches exposure at home	<i>0.58 b.l.</i>	1.05	---	0.71	1.13	1.20	1.65
Indoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	1.04	0.87	---	1.52*	1.39	1.12	1.12
Outdoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	1.10	1.57 **	---	1.01	0.94	0.94	0.82

AR: allergic rhinitis; # computed by physician visits; °computed only in subjects with asthma/AR diagnosis

Adjusted for sex, age, BMI, study attendance; p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05

Table 32b. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Eczema	AR diagnosis	AR symptoms	Severe AR##°
Passive smoke exposure	0.99	1.40*	1.01	1.32	<i>1.29b.l.</i>	1.14
Asthma/allergic rhinitis familiarity	2.58***	1.56**	1.43*	2.66***	2.03***	0.82
Childhood respiratory infections	3.54***	5.28***	1.26	1.11**	1.50**	0.99
Pets exposure at home	1.52*	1.08	0.85	1.48*	<i>0.78b.l.</i>	1.32
Cockroaches exposure at home	0.87	1.27	1.05	1.21	1.23	1.15
Indoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	1.17	0.91	0.98	1.16	1.09	0.98
O ₃ $\geq 75^\circ$ perc. #	0.54*	0.38***	0.60*	0.46*	1.04	0.86
NO ₂ $\geq 75^\circ$ perc. #	0.90	0.73	0.63*	0.66	1.27	0.43*
PM ₁₀ $\geq 75^\circ$ perc. #	---	---	---	---	---	---
PM _{2.5} $\geq 75^\circ$ perc. #	<i>0.54b.l.</i>	0.84	1.08	<i>0.56b.l.</i>	0.86	3.20**

AR: allergic rhinitis; ## computed by physician visits; °computed only in subjects with asthma/AR diagnosis; #75° percentile: O₃ 48.7 $\mu\text{g}/\text{m}^3$; NO₂ 60.7 $\mu\text{g}/\text{m}^3$;

PM₁₀ 42.3 $\mu\text{g}/\text{m}^3$; PM_{2.5} 24.0 $\mu\text{g}/\text{m}^3$

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 32c. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Eczema	AR diagnosis	AR symptoms	Severe AR##°
Passive smoke exposure	0.98	1.45**	1.06	1.41*	1.31*	1.25
Asthma/allergic rhinitis familiarity	2.50***	1.49**	1.41*	2.78***	2.24***	0.88
Childhood respiratory infections	3.65***	5.65***	1.19	0.98	1.72***	0.86
Pets exposure at home	1.52*	1.05	1.02	1.43*	0.70**	1.27
Cockroaches exposure at home	0.86	1.18	1.02	1.27	1.30	1.37
Indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	1.29	1.00	<i>1.34b.l.</i>	1.30	0.94	0.96
Cluster: Only NO ₂ $\geq 75^\circ$ perc. # PM ₁₀ & PM _{2.5} $\geq 75^\circ$ perc. # (ref. only O ₃ $\geq 75^\circ$ perc. #)	1.17 0.61	1.13 0.91	0.91 0.90	0.90 0.50*	1.14 1.02	0.43* 1.38

AR: allergic rhinitis; ## computed by physician visits; ° computed only in subjects with asthma/AR diagnosis; #75° percentile: O₃ 48.7 $\mu\text{g}/\text{m}^3$; NO₂ 60.7 $\mu\text{g}/\text{m}^3$; PM₁₀ 42.3 $\mu\text{g}/\text{m}^3$; PM_{2.5} 24.0 $\mu\text{g}/\text{m}^3$

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table 32d. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) (interaction between allergens and air pollution) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	Severe AR##°
<i>Interaction between allergens and indoor PM_{2.5} concentration at school</i>							
Only pets exposure at home	0.66	1.03	---	1.03	1.47	0.50 ***	1.24
Only cockroaches exposure at home	0.82	0.82	---	0.83	0.72	0.99	1.20
Only indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.77	0.99	---	1.43 *	1.33	0.80	0.89
Pets exposure at home * indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	2.36*	0.85	---	0.83	<i>0.52b.l.</i>	1.72*	0.69
Cockroaches exposure at home * indoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.93	1.52	---	0.89	1.67	1.26	1.51
<i>Interaction between allergens and outdoor PM_{2.5} concentration at school</i>							
Only pets exposure at home	0.77	0.88	---	1.01	0.82	0.61 *	1.05
Only cockroaches exposure at home	<i>0.47 b.l.</i>	0.90	---	<i>0.60 b.l.</i>	0.92	1.23	<i>1.98 b.l.</i>
Only outdoor PM _{2.5} concentration at school ≥ 25 $\mu\text{g}/\text{m}^3$	0.87	1.29	---	1.13	0.65	0.91	0.84

Pets exposure at home * outdoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	1.53	1.21	---	0.86	1.96	1.33	1.19
Cockroaches exposure at home * outdoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	1.78	1.33	---	1.48	1.99	0.93	0.57

AR: allergic rhinitis; ## computed by physician visits; ° computed only in subjects with asthma/AR diagnosis

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; adjusted for sex, age, BMI, passive smoke, asthma/allergic rhinitis familiarity, childhood respiratory infections, study attendance

Table 32e1. Risk factors for lifetime asthma symptoms/diagnosis stratified by air pollutants concentration. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Asthma		Wheeze	
		< 75° perc.#	$\geq 75^\circ$ perc.#	< 75° perc.#	$\geq 75^\circ$ perc.#
Asthma/allergic rhinitis familiarity	O ₃	2.32***	3.45**	1.52**	1.40
	NO ₂	2.48***	3.22**	1.42**	2.20***
	PM ₁₀	2.50***	9.00**	1.62***	2.07*
	PM _{2.5}	2.37***	4.09**	1.50**	1.86*
Passive smoke exposure	O ₃	1.01	0.73	1.39*	1.54
	NO ₂	1.08	0.71	1.35*	1.34
	PM ₁₀	1.10	0.27	<i>1.28b.l.</i>	2.00*
	PM _{2.5}	1.16	0.72	<i>1.35b.l.</i>	1.74*
Childhood respiratory infections	O ₃	3.09***	8.56***	5.51***	7.24***
	NO ₂	3.62***	5.66***	6.73***	6.31***
	PM ₁₀	3.73***	7.16**	7.00***	4.97***
	PM _{2.5}	3.09***	7.66***	5.34***	4.47***
Pets exposure at home	O ₃	<i>1.51b.l.</i>	1.28	1.12	0.67
	NO ₂	1.14	2.07*	1.04	0.95
	PM ₁₀	1.33	<i>2.72b.l.</i>	1.06	0.85
	PM _{2.5}	1.32	1.57	1.06	0.93
Cockroaches exposure at home	O ₃	0.77	0.97	1.11	1.26
	NO ₂	0.81	0.75	0.98	1.24
	PM ₁₀	0.91	0.19	0.99	1.05
	PM _{2.5}	1.05	0.89	1.13	1.26
Indoor PM _{2.5} concentration at school $\geq 25 \mu\text{g}/\text{m}^3$	O ₃	1.05	1.09	0.69*	1.24
	NO ₂	1.16	0.64	0.96	0.94
	PM ₁₀	1.20	---	1.06	---
	PM _{2.5}	1.17	---	0.91	---

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 $\mu\text{g}/\text{m}^3$; NO₂ 60.7 $\mu\text{g}/\text{m}^3$; PM₁₀ 42.3 $\mu\text{g}/\text{m}^3$; PM_{2.5} 24.0 $\mu\text{g}/\text{m}^3$

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI and familiarity

Table 32e2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants concentration. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Eczema		AR diagnosis		AR symptoms		Severe AR##°	
		< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#
Asthma/allergic rhinitis familiarity	O ₃	1.37b.l.	1.76b.l.	2.96***	4.46***	1.93***	3.29***	0.81	0.83
	NO ₂	1.41*	1.80*	2.35***	4.87***	2.23***	2.08***	0.93	1.66
	PM ₁₀	1.59**	1.13	2.67***	4.67**	2.37***	1.59	0.96	2.07
	PM _{2.5}	1.48*	1.45	2.57***	3.92***	2.31***	1.79*	0.68	1.52
Passive smoke exposure	O ₃	0.98	0.97	1.32	1.08	1.28	1.45	1.18	1.16
	NO ₂	1.02	0.49*	1.85**	0.52b.l.	1.11	1.45b.l.	1.50	0.94
	PM ₁₀	1.23	0.38*	1.63**	0.25b.l.	1.13	1.73b.l.	1.33	1.86
	PM _{2.5}	1.21	0.61	1.52*	0.79	1.17	1.48	0.96	1.03
Childhood respiratory infections	O ₃	1.19	1.97*	1.06	1.62	1.64**	1.72*	1.04	0.87
	NO ₂	1.38*	1.24	0.94	1.62	1.70***	1.78**	0.74	1.91
	PM ₁₀	1.01	1.64	0.98	2.33b.l.	1.74***	1.85*	0.80	1.60
	PM _{2.5}	1.18	1.58b.l.	0.96	1.44	1.48*	1.79*	0.82	1.55
Pets exposure at home	O ₃	0.93	0.95	1.78**	0.55	0.85	0.42**	1.37	1.17
	NO ₂	1.21	0.90	1.62*	0.94	0.66**	0.89	1.26	0.94
	PM ₁₀	1.16	0.81	1.60**	0.71	0.74*	0.62	1.27	1.05
	PM _{2.5}	0.86	0.99	1.50*	0.93	0.79	0.65b.l.	1.39	1.11
Cockroaches exposure at home	O ₃	0.94	0.96	1.22	0.72	1.39	1.03	1.19	3.39
	NO ₂	0.77	0.84	0.95	1.42	0.99	1.39	1.37	2.39b.l.
	PM ₁₀	0.77	0.74	0.97	2.61b.l.	1.04	1.47	1.21	2.66
	PM _{2.5}	1.03	1.18	1.00	2.39*	1.15	1.56b.l.	0.61	3.24*
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	O ₃	0.85	2.20*	0.93	1.57	1.16	0.96	0.88	1.27
	NO ₂	1.33b.l.	1.04	1.33	0.61	0.96	0.83	0.93	2.51
	PM ₁₀	1.33b.l.	---	1.39b.l.	---	1.00	---	0.87	---
	PM _{2.5}	0.95	---	1.20	---	1.18	---	1.00	---

AR: allergic rhinitis; SPT: skin prick test positivity; # computed by physician visits; °computed only in subjects with asthma/AR diagnosis; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI and familiarity

Table 32f1. Risk factors for lifetime asthmatic symptoms/diseases stratified by air pollutants cluster. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Combined effect")

<i>Risk factors</i>	Asthma			Wheeze		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	2.22 <i>b.l.</i>	2.28***	9.00**	2.59**	1.21	2.07*
Passive smoke exposure	0.81	1.05	0.27	0.85	1.50*	2.0*
Childhood respiratory infections	5.37***	3.11***	7.16**	9.20***	5.43***	4.97***
Pets exposure at home	2.17	1.14	2.72 <i>b.l.</i>	1.17	1.02	0.85
Cockroaches exposure at home	1.55	0.85	0.19	1.23	1.09	1.05
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	0.84	1.28	---	1.23	0.94	---

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI and familiarity

Table 32f2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants cluster. Cumulative analyses on CCM and EDEN subsample. Results of the logistic regression analysis (OR) ("Combined effect")

<i>Risk factors</i>	Eczema			AR diagnosis			AR symptoms			Severe AR##°		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	3.03**	1.22	1.13	6.43***	2.42***	4.67**	2.97***	2.39***	1.59	2.53	0.70	2.07
Passive smoke exposure	0.62	1.42 <i>b.l.</i>	0.38*	0.57	1.79**	0.25 <i>b.l.</i>	1.15	1.21	1.73 <i>b.l.</i>	0.47	1.16	1.86
Childhood respiratory infections	0.98	1.16	1.64	1.37	0.80	2.33 <i>b.l.</i>	1.92*	1.70**	1.85*	1.06	0.69	1.60
Pets exposure at home	0.91	1.04	0.81	1.13	1.44 <i>b.l.</i>	0.71	1.39	0.60**	0.62	0.47	1.23	1.05
Cockroaches exposure at home	0.85	1.17	0.74	1.92	1.12	2.61 <i>b.l.</i>	1.30	1.15	1.47	1.20	1.02	2.66
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	0.94	1.32	---	0.88	1.28	---	1.13	0.97	---	0.52	0.88	---

AR: allergic rhinitis; SPT: skin prick test positivity; # computed by physician visits; °computed only in subjects with asthma/AR diagnosis; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI and familiarity

GENERAL POPULATION SAMPLES

Table 33. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Cumulative analyses in IMCA and PISA2 subsample. Results of the logistic regression analysis (OR) ("*Independent effect*")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms	AO	Blood eosinophilia
Passive smoke exposure	0.98	n.a.	n.a.	1.05	1.14	n.a.	0.84	1.12
Pets exposure at home	1.10	n.a.	n.a.	1.00	0.96	n.a.	1.15	1.06
Vehicular traffic near home	1.30 *	n.a.	n.a.	<i>1.17 b.l.</i>	1.03	n.a.	1.03	1.19
Work exposure	1.13	n.a.	n.a.	1.45 ***	1.32 **	n.a.	<i>1.28 b.l.</i>	1.10

AR: allergic rhinitis; AO: airway obstruction

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for BMI, age, sex, educational level and smoking habits

STEP 3

CHILDREN SAMPLES

Table 34a. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("*Independent effect*")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Passive smoke exposure	1.06	1.28***	1.08	0.93	0.94	1.05
Asthma/allergic rhinitis familiarity	2.19***	1.57***	1.41***	1.47***	2.14***	1.76***
Allergens exposure at home	0.97	0.98	1.22***	1.09	1.20*	1.11*

AR: allergic rhinitis

Adjusted for sex, age, study attendance; p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05

Table 34b. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("*Independent effect*")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Passive smoke exposure	1.06	1.29***	<i>1.09 b.l.</i>	0.94	0.92	1.06
Asthma/allergic rhinitis familiarity	2.17***	1.53***	1.38***	1.44***	2.09***	1.73***
Allergens exposure at home	1.01	0.98	1.23***	1.08	1.22**	1.13*
O ₃ ≥ 75° perc. #	0.97	1.60	0.71	0.50*	1.62	1.95*
NO ₂ ≥ 75° perc. #	1.14	1.70	0.72	0.53*	1.82	2.46**
PM ₁₀ ≥ 75° perc. #	0.61	0.85	0.96	1.17	0.76	0.77

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34c. Risk factors for lifetime asthmatic and allergic symptoms/diseases. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Independent effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Passive smoke exposure	1.06	1.29***	<i>1.09 b.l.</i>	0.93	0.92	1.06
Asthma/allergic rhinitis familiarity	2.17***	1.53***	1.38***	1.44***	2.09***	1.73***
Allergens exposure at home	1.01	0.98	1.23***	1.08	1.22**	1.13*
Cluster:						
Only NO ₂ ≥ 75° perc. #	1.18	1.09	0.99	1.01	1.15	1.31*
PM ₁₀ & PM _{2.5} ≥ 75° perc. # (ref. only O ₃ ≥ 75° perc. #)	0.72	0.93	0.94	1.17	0.87	1.02

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34d1. Risk factors for lifetime asthma symptoms/diagnosis stratified by air pollutants concentration. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Asthma		Wheeze		Dry cough	
		< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#
Asthma/allergic rhinitis familiarity	O ₃	2.11***	3.06***	1.50***	1.94**	1.37***	1.82*
	NO ₂	2.13***	2.83***	1.49***	2.50***	1.42***	1.29
	PM ₁₀	2.14***	5.63**	1.56***	2.21**	1.39***	1.88
	PM _{2.5}	1.52**	4.04**	1.35**	1.86**	1.08	1.98*
Passive smoke exposure	O ₃	1.05	1.26	1.25***	2.26***	1.07	1.35
	NO ₂	1.05	1.07	1.27***	1.51*	1.08	1.05
	PM ₁₀	1.06	0.71	1.26***	1.96*	1.09	1.19
	PM _{2.5}	1.04	1.10	1.34**	1.61*	1.36	0.79
Allergens exposure at home	O ₃	1.01	1.04	1.02	0.56**	1.26***	0.74
	NO ₂	0.98	1.04	0.97	1.11	1.24***	0.92
	PM ₁₀	0.98	0.92	0.97	1.06	1.23***	1.04
	PM _{2.5}	0.96	0.85	0.80*	1.37	0.93	1.08

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34d2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants concentration. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Air pollutants	Eczema		AR diagnosis		AR symptoms	
		< 75° perc.#	≥75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#
Asthma/allergic rhinitis familiarity	O ₃	1.42***	1.74**	2.03***	3.50***	1.63***	3.17***
	NO ₂	1.40***	1.98***	1.96***	4.33***	1.69***	2.27***
	PM ₁₀	1.45***	<i>1.72 b.l.</i>	2.04***	4.60**	1.74***	1.99**
	PM _{2.5}	1.39**	1.69*	1.95***	4.27***	1.73***	2.19***
Passive smoke exposure	O ₃	0.92	1.12	0.92	1.27	1.05	1.36
	NO ₂	0.95	0.79	0.97	0.67	1.03	<i>1.37 b.l.</i>
	PM ₁₀	0.95	<i>0.44 b.l.</i>	0.95	<i>0.23 b.l.</i>	1.03	1.57
	PM _{2.5}	0.97	0.65	1.01	0.70	0.99	1.47
Allergens exposure at home	O ₃	<i>1.10 b.l.</i>	0.97	1.24**	0.90	1.15**	0.85
	NO ₂	<i>1.11 b.l.</i>	0.96	1.21*	1.17	1.11*	1.18
	PM ₁₀	1.08	1.04	1.22**	1.02	1.11*	1.13
	PM _{2.5}	1.89	1.27	1.19	0.87	1.03	1.15

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34e1. Risk factors for lifetime asthmatic symptoms/diseases stratified by air pollutants cluster. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Combined effect")

Risk factors	Asthma			Wheeze			Dry cough		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	2.21*	2.10***	5.63**	3.19***	1.43***	2.21**	1.18	1.38***	1.88
Passive smoke exposure	1.18	1.06	0.71	1.16	1.28***	1.96*	0.88	<i>1.10 b.l.</i>	1.19
Allergens exposure at home	0.87	1.02	0.92	1.20	0.97	1.06	0.87	1.23***	1.04

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34e2. Risk factors for lifetime allergic symptoms/diseases stratified by air pollutants cluster. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Combined effect")

<i>Risk factors</i>	Eczema			AR diagnosis			AR symptoms		
	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #)	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
Asthma/allergic rhinitis familiarity	2.24*	1.38***	<i>1.72 b.l.</i>	4.72***	1.92***	4.60**	2.90***	1.66***	1.99**
Passive smoke exposure	0.74	0.96	<i>0.44 b.l.</i>	0.80	0.95	<i>0.23 b.l.</i>	1.37	1.04	1.57
Allergens exposure at home	0.91	1.09	1.04	1.51	1.23**	1.02	<i>1.11</i>	1.12*	1.13

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age

Table 34f. Groups of exposure as risk factors for lifetime asthmatic and allergic symptoms/diseases. Analyses on cumulative children sample. Results of the logistic regression analysis (OR) ("Combined effect")

	Asthma	Wheeze	Dry cough	Eczema	AR diagnosis	AR symptoms
Cluster 2	0.81	1.01	0.87	1.41*	0.85	0.91
Cluster 3	0.88	1.25*	0.71*	1.34*	0.63**	0.70***

Adjusted for sex, age and study attendance

Cluster 1 as reference category

Cluster 1: subjects exposed to only allergens;

Cluster 2: subjects with asthmatic/allergic disease familiarity and exposed to allergens and high level of O₃ concentration (≥ 75° percentile);

Cluster 3: subjects with asthmatic/allergic disease familiarity and exposed to allergens and high levels of air pollutants concentration (≥ 75° percentile) (PM₁₀, PM_{2.5}, NO₂)

Table A. Summary of the available data in each of the pre-existing study used for the statistical analyses

	General population samples					Children samples					
	PISA1 1985- 1988	PISA2 1991- 1993	IMCA 2009- 2011	SEASD 1997-98	CHIS2000 2001-2002	CMM 2010- 2014	REPRO_PL 2006 - 2015	MAAS 1997-2014	EPITEEN 2003-2004	G21 2005-2006 2009-2012 2012-2014	EDEN 2003-2013
Country	Italy	Italy	Italy	Italy	Spain	Italy	Poland	UK	Portugal	Portugal	France
Population	General pop.	General pop.	Adult	Adult women	Adults	Children	Children	Children	Children	Children	Children
GENERAL CHARACTERISTICS by questionnaire											
sex											
age											
BMI											
Educational level											
HEALTH DATA by questionnaire											
Asthma											
Asthma severity											
Wheeze											
Dry cough											
Allergic rhinitis diagnosis											
Allergic rhinitis severity											
Allergic rhinitis symptoms											
Eczema ever diagnosed											
BIOMARKERS by instrumental measurements											
Results of skin prick tests											
Ige total											
Concentration of blood eosinophils											
Results of bronchial hyper-responsiveness assessment											
Spirometry results											
RISK FACTORS/EXPOSURE DATA by questionnaire											
Smoking habits											
Passive smoke exposure											
Asthma/allergic rhinitis familiarity											
Childhood respiratory infections											
Work exposure											
Mould exposure at home											
Pets exposure at home											
Cockroaches exposure at home											
Carpets at home											
Home distance ≤100m from road											

Air pollution sources near home											
Vehicular traffic near home											
Air pollution sources near school											
EXPOSURE DATA by instrumental measurements											
Indoor PM _{2.5} concentration at school											
Outdoor PM _{2.5} concentration at school											
Biological allergens concentration in dust samples											
Air quality monitoring stations data											
O ₃											
NO ₂											
PM ₁₀											
PM _{2.5}											

in green: data from general population samples; in blu: data from children samples

	Asthma					Wheeze				Dry cough				Eczema						AR diagnosis					AR symptoms					Severe AR		SPT					
	C C M	E D E N	G 2 1	C C M + E D E N	C C M + R E P R O	C C M	G 2 1	C C M + R E P R O	C C M + E D E N	C C M	E D E N	G 2 1	C C M + R E P R O	C C M	E P I T E E N	E D E N	R E P R O - P L	G 2 1	C C M + E D E N	C C M + R E P R O	C C M	E P I T E E N	G 2 1	C C M + R E P R O	C C M + E D E N	C C M	E P I T E E N	R E P R O - P L	G 2 1	C C M + R E P R O	C C M + E D E N	C C M	C C M + E D E N	C C M	C C M + R E P R O		
Disease familiarity and childhood infections																																					
Asthma/allergic rhinitis familiarity																																					
Childhood respiratory infections																																					
Allergens																																					
Mould exposure at home																																					
Pets exposure at home																																					
Cockroaches exposure at home																																					
Carpets at home																																					
Air pollution exposure																																					
Passive smoke exposure																																					
Home distance ≤100m from road																																					
Air pollution sources near home																																					
Air pollution sources near school																																					
Indoor PM _{2.5} concentration at school ≥25 µg/m ³																																					
Outdoor PM _{2.5} concentration at school ≥25 µg/m ³																																					
Outdoor PM _{2.5} concentration ≥ 75° percentile																																					
Outdoor PM ₁₀ concentration ≥ 75° percentile																																					
Outdoor NO ₂ concentration ≥ 75° percentile																																					
Outdoor O ₃ concentration ≥ 75° percentile																																					
Only outdoor NO ₂ concentration ≥ 75° percentile																																					
PM ₁₀ &PM _{2.5} concentration ≥ 75° percentile																																					

Table B. Summary of the results of the logistic regression analyses in children samples (*models without interaction*) (“Independent effect”)

in red: significant risk factor; in orange: border line risk factor; in green: significant protective factor; in light green: borderline protective factors
AR: allergic rhinitis; SPT: skin prick test

Table C. Summary of the results of the logistic regression analyses in general population sample (*models without interaction*) (“*Independent effect*”)

	Asthma				Wheeze			Dry cough			Eczema				AR diagnosis					AR symptoms	Severe asthma	Severe AR	AO			BHR	Blood eosinophilia	SPT
	PISA1	PISA2	IMC + PISA2	SEASD	PISA1	PISA2	SEASD	PISA1	PISA2	SEASD	PISA2	IMC	SEASD	IMC + PISA2	PISA1	PISA2	IMC	CHIS	IMC + PISA2	IMCA	PISA2	PISA2	PISA2	IMC + PISA2	IMC + PISA2	PISA2	PISA2	PISA2
<i>Disease familiarity and childhood infections</i>																												
Asthma/allergic rhinitis familiarity																												
Childhood respiratory infections																												
<i>Allergens</i>																												
Pets exposure at home																												
<i>PM exposure</i>																												
Work exposure																												
Passive smoke exposure																												
Home distance ≤100m from road																												
Air pollution sources near home																												
Vehicular traffic near home																												

in red: significant risk factor; in orange: border line risk factor; in green: significant protective factor; in light green: borderline protective factors
AR: allergic rhinitis; BHR: bronchial hyper-responsiveness; SPT: skin prick test

Table D. Summary of the results of the logistic regression analyses in children samples (*models with interaction*) (“*Combined effect*”)

	Asthma		Wheeze	Dry cough	Eczema				AR diagnosis	AR symptoms			Severe AR	SPT		IgE	Blood eosinophilia	
	C C M	CC M+E DEN	CCM	CCM	C C M	E D E N	RE PR O_ PL	CC M +E DE N	CCM	CC M	EDE N	C C M + E D E N	C C M	C C M + E D E N	C C M	C C M + R E P R O	EDE N	EDEN
Only allergens exposure																		
Mould exposure at home																		
Pets exposure at home																		
Cockroaches exposure at home																		
Carpets at home																		
Only air pollution exposure																		
Home distance ≤100m from road																		
Air pollution sources near home																		
Air pollution sources near school																		
Indoor PM _{2.5} concentration at school ≥25 µg/m ³																		
Outdoor PM _{2.5} concentration at school ≥25 µg/m ³																		
Combined exposure to allergens and air pollution																		
Mould exposure at home with air pollution sources near home																		
Air pollution sources near home with mould exposure at home																		
Pets exposure at home with air pollution sources near home																		
Pets exposure at home with indoor PM _{2.5} concentration at school																		
Indoor PM _{2.5} concentration at school with pets exposure at home																		
Indoor PM _{2.5} concentration at school with carpets at home																		
Cockroaches exposure at home with outdoor PM _{2.5} concentration at school																		
Mould exposure at home with outdoor PM _{2.5} concentration at school																		
Outdoor PM _{2.5} concentration at school with Mould exposure at home																		
Outdoor PM _{2.5} concentration at school with carpets at home																		

AR:

allergic rhinitis; SPT: skin prick test; In red: significant risk factor; in orange: border line risk factor; in green: significant protective factor; in light green: borderline protective factors

Table E1. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

		Asthma										
		O ₃		NO ₂		PM ₁₀		PM _{2.5}		Air pollutants exposure cluster		
	<i>TOTAL</i>	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	0.99											
Asthma/allergic rhinitis familiarity	3.36 ***	-	+	-	+	-	+	-	+	-	+	++
Mould exposure at home	1.22											
Pets exposure at home	1.16											
Cockroaches exposure at home	0.85											
Carpets at home	0.37 ***	-	+	+	-	+		+		+	-	
Air pollution sources near home	0.79											
CCM & EDEN												
Passive smoke exposure	0.74											
Asthma/allergic rhinitis familiarity	3.17 ***	-	+	-	+	-	+	-	+		-	+
Childhood respiratory infections	5.15 ***	-	+	-	+	-	+	-	+	+	-	++
Pets exposure at home	0.93				+							
Cockroaches exposure at home	<i>0.58 b.l.</i>											
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	1.04											
Outdoor PM _{2.5} concentration at school ≥25 µg/m ³	1.10											
Children cumulative sample												
Passive smoke exposure	1.06											
Asthma/allergic rhinitis familiarity	2.19***	-	+	-	+	-	+	-	+	+	-	++
Allergens exposure at home	0.97											

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table

Table E2. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

	Wheeze											
		O ₃		NO ₂		PM ₁₀		PM _{2.5}		Air pollutants exposure cluster		
	TOTAL	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	1.40*	-	+	-			+		+		+	++
Asthma/allergic rhinitis familiarity	1.97 ***									++	-	+
Mould exposure at home	1.20	+										
Pets exposure at home	1.00											
Cockroaches exposure at home	1.15											
Carpets at home	0.64 ***		+	+		+		+			+	
Air pollution sources near home	0.95				+							
CCM & EDEN												
Passive smoke exposure	1.21 **						+		+		+	++
Asthma/allergic rhinitis familiarity	1.56 **	-		-	+	+	++	-	+	++		+
Childhood respiratory infections	6.59 ***	-	+	+	-	+	-	-	--	+	-	--
Pets exposure at home	0.96											
Cockroaches exposure at home	1.05											
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	0.87											
Children cumulative sample												
Passive smoke exposure	1.28***	-	+	-	+	-	+	+	++		=	+
Asthma/allergic rhinitis familiarity	1.57***	-	+	-	+	-	+	-	+	++	-	=
Allergens exposure at home	0.98		+					+				

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI

-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table

Table E3. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

	Dry cough
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		O ₃		NO ₂		PM ₁₀		PM _{2.5}		Air pollutants exposure cluster		
	<i>TOTAL</i>	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	1.14											
Asthma/allergic rhinitis familiarity	1.76 **	-	+	+		-					+	
Mould exposure at home	<i>1.4 b.l.</i>			+								
Pets exposure at home	0.57 **	+		+		-		+			+	
Cockroaches exposure at home	1.54 *	+			+		+	++	+			+
Carpets at home	0.95											
Air pollution sources near home	1.10											
Children cumulative sample												
Passive smoke exposure	1.08											
Asthma/allergic rhinitis familiarity	1.41***	-	+	+		-			+		-	
Allergens exposure at home	1.22***	+		+		+					+	

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table

Table E4. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

	Eczema											
		O ₃		NO ₂		PM ₁₀		PM _{2.5}		Air pollutants exposure cluster		
	<i>TOTAL</i>	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #

CCM & REPRO_PL												
Passive smoke exposure	0.85						+		+			+
Asthma/allergic rhinitis familiarity	1.74***	-	+	-	+	+		-		+	-	
Mould exposure at home	1.19	+							+			
Pets exposure at home	0.99											
Cockroaches exposure at home	0.89											
Carpets at home	0.83											
Air pollution sources near home	<i>1.44b.l.</i>											
CCM & EDEN												
Passive smoke exposure	0.88				+		+					+
Asthma/allergic rhinitis familiarity	1.57 **			-	+	+		-		+		
Childhood respiratory infections	1.29		+									
Pets exposure at home	0.94											
Cockroaches exposure at home	0.71											
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	1.52*		+									
Children cumulative sample												
Passive smoke exposure	0.93											
Asthma/allergic rhinitis familiarity	1.47***	-	+	-	+	-		-	+	+	-	
Allergens exposure at home	1.09											

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table

Table E5. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

AR diagnosis												
		O ₃		NO ₂		PM ₁₀		PM2.5		Air pollutants exposure cluster		
	TOTAL	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	1.08											

Asthma/allergic rhinitis familiarity	4.19 ***	++	+	-	+	-	+	--	-	++	=	+
Mould exposure at home	1.16											
Pets exposure at home	1.01											
Cockroaches exposure at home	1.11						+		+			+
Carpets at home	0.65 *											
Air pollution sources near home	0.85											
CCM & EDEN												
Passive smoke exposure	0.96			+		+		+			+	
Asthma/allergic rhinitis familiarity	4.82**	--	-	-	+	--	-	--	-	+	--	-
Childhood respiratory infections	1.77*											
Pets exposure at home	1.13	+		+		+		+				
Cockroaches exposure at home	1.13								+			
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	1.39											
Children cumulative sample												
Passive smoke exposure	0.94											
Asthma/allergic rhinitis familiarity	2.14***	-	+	-	+	-	+	-	+	++	-	+
Allergens exposure at home	1.20*	+		+		+				+		

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³

p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1> p-value >0.05; Adjusted for sex, age, BMI

-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table

Table E6. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

Table 2b: Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration												
	AR symptoms											
		O ₃		NO ₂		PM ₁₀		PM _{2.5}		Air pollutants exposure cluster		
	TOTAL	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	1.26*	+			+							
Asthma/allergic rhinitis familiarity	2.64 ***	-	+	+	-	+	-	+	-	+	++	*
Mould exposure at home	1.39 *	+			+	=						
Pets exposure at home	0.73**		+	+		-					+	

Cockroaches exposure at home	1.05											
Carpets at home	0.94											
Air pollution sources near home	1.03											
CCM & EDEN												
Passive smoke exposure	0.99											
Asthma/allergic rhinitis familiarity	2.02 ***	-	+	++	+	+		+	-	++	+	
Childhood respiratory infections	1.70 ***	-	+	=	+	+	++	-	+	++	=	+
Pets exposure at home	0.68 *		+	+		-					+	
Cockroaches exposure at home	1.20											
Indoor PM _{2.5} concentration at school ≥25 µg/m ³	1.12											
Children cumulative sample												
Passive smoke exposure	1.05											
Asthma/allergic rhinitis familiarity	1.76***	-	+	-	+	-	+	-	+	++	-	+
Allergens exposure at home	1.11*	+		=		=					+	

AR: allergic rhinitis; SPT: skin prick test positivity; #75° percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI

Table E7. Summary of the results of the logistic regression analyses in children samples stratified by air pollutants concentration

		Skin Prick Test positivity										
		O₃		NO₂		PM₁₀		PM_{2.5}		Air pollutants exposure cluster		
	<i>TOTAL</i>	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	< 75° perc.#	≥ 75° perc.#	only NO ₂ ≥ 75° perc.	only O ₃ ≥ 75° perc. #	PM ₁₀ & PM _{2.5} ≥ 75° perc. #
CCM & REPRO_PL												
Passive smoke exposure	1.10		+									
Asthma/allergic rhinitis familiarity	2.09 ***	-	+	+	-	+		+		-	+	
Mould exposure at home	1.01											
Pets exposure at home	0.83											
Cockroaches exposure at home	0.95											
Carpets at home	0.68 **		+	+		+		+			+	
Air pollution sources near home	1.00											

AR: allergic rhinitis; SPT: skin prick test positivity; #75^o percentile: O₃ 48.7 µg/m³; NO₂ 60.7 µg/m³; PM₁₀ 42.3 µg/m³; PM_{2.5} 24.0 µg/m³
p-value: * <0.05 ; ** <0.01; *** <0.001; b.l.: 0.1 > p-value >0.05; Adjusted for sex, age, BMI
-: OR values lower than the cumulative one reported in the table; +: OR values higher than the cumulative one reported in the table