

Adult onset of asthma and proximity to traffic

A Nested SAPALDIA Project in collaboration of SAPALDIA with CREAL

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Background and Hypotheses

Air pollution triggers asthma exacerbations in children and adults. Most recent evidence point in the direction that living close to busy traffic arteries may cause the onset of asthma in children. Onset of asthma in adults is in general far less investigated and studies on air pollution and asthma onset are very rare. ECRHS finds suggestive associations between asthma incidence and reported traffic (N is ~ 4300 subjects available for the incidence study). Reported traffic is, however, a very questionable measure of exposure. In a much smaller sample - due to lack of home-based exposure data – a preliminary positive correlation between asthma onset and home outdoor NO₂ is also present. In a recent collaboration with Imperial College ECRHS has now linked all subjects home location with a geostatistical model created to estimate NO₂ maps all across Europe (APMOSPHERE model of D. Briggs and others). Thus, the sample size with estimates of local traffic is now larger. Associations with incidence of asthma remain suggestive, of borderline significance. The only clearly significant finding relates to the association between these home outdoor measures of NO₂ and the asthma symptom score at follow-up among those with no asthma at all at baseline. However, the APMOSPHERE model is not optimal as it has not been developed to characterize the contrasts of pollution along streets. Moreover, ECRHS has no valid information about the historic levels of pollution (at ECRHS I), thus information about change in exposure is not available.

SAPALDIA is in the unique position to investigate the hypothesis that subjects living in high traffic density neighbourhoods are more likely to develop asthma (adult onset asthma). Given that adult onset asthma may be a partly different phenotype than childhood asthma, evidence of a contribution of traffic related pollution to asthma incidence in children cannot be simply extrapolate to adults.

The enclosed project thus proposes to investigate the hypothesis that adult onset of asthma to be related to peoples' exposure to ambient air pollution, and in particular to primary emissions from traffic which are known to exert particularly high concentrations along busy roads. We further hypothesize that, as suggested – albeit inconsistently - in some childhood studies, individual factors such as sex, atopy, a family history of asthma, or bronchial reactivity at baseline, or a proxy measure of small airways (indicated with low FEF₂₅₋₇₅/FVC at baseline) to modify the association between pollution and incidence of asthma. The objective of the nested project is to conduct the analyses to investigate the main hypothesis and to write up the results in at least one manuscript.

Methods

Outcome definitions

Subjects without doctors diagnosed asthma nor COPD in SAPALDIA 1 may be used as the core population. As there are several ways of defining 'disease free status' at baseline and 'onset of asthma' at follow-up, more than one definition of asthma incidence may be used. To provide comparable results, definitions as well as analytical approaches will include those used in ECRHS (see incidence analysis in attached submitted work). The working group of this nested project will make final decisions as part of the work.

Markers of exposure to air pollution:

Exposure to local traffic related pollutants has been characterized in numerous ways in recent studies on asthma onset or asthma prevalence and pollution in children. The general concepts consist in the use of markers such as traffic density, type of traffic, distance of residences to roads of various density, and/or

the local modelling of pollutants taken as markers of local traffic, e.g. NO₂. However, details of methods are heterogeneous across projects, thus difficult to quantitatively compare or integrate.

This SAPALDIA project proposes the use of the markers of exposure previously used in SAPALDIA analyses rather than the derivation of any other marker. The prime candidates are three exposure terms developed and used in Bayer-Oglesby et al (Am J Epi 2006) as well as modelled traffic PM₁₀ as used in the lung function analyses (Downs et al, submitted to NEJM).

Details of the required parameters are provided in the Annex. While the Annex table lists more than 40 markers of exposure per subject, it is of note that not all of them will be used from the beginning. Some may be candidates for sensitivity analyses, if at all, or explorative steps of the main analyses. It is however thus most efficient to include those listed in the data.

The prime markers of interest are the following:

- distance to main road at baseline and follow-up
- length of main street segment within 200m at baseline and follow-up,
- main street within 20m (Y/N) at baseline and follow-up
- traffic PM₁₀
- NO₂

Other markers will be useful in expanded analyses (such as total PM₁₀ or secondary PM₁₀ for which null results are expected.

Subjects who did not move since SAPALDIA 1 are of particular interest, thus the variable 'moved between SAPALDIA 1 and 2' needs to be on the data set.

In this project – in contrast to the lung function analyses - cumulative (or average) exposure is expected to be more important than the 'change' but this needs to be addressed.

Susceptibility factors will be tested in a second stage of the analysis. These steps may remain in a preliminary phase with priority given to the above main analyses and write-up.

We are also aware of the fact that the asthma symptom score may be used to investigate effects of air pollution among asthmatics. However, the interpretation of it is currently ambiguous and may be seen as a measure of the outcome course of asthma ('severity'). Given the abundant evidence of adverse effects of pollution on asthma exacerbations, this analysis will not receive high priority.

Organization of work and data

The statistical analyses will be conducted by Raquel Garcia at CREAL, under the lead of Nino Kuenzli, and in collaboration with all interested partners of SAPALDIA, which at this point in time have been listed as being Thierry Rochat, Pierre-Olivier Bridevaux, Margaret Gerbase, Sally Liu and Christian Schindler. Raquel Garcia is a technician with a Master in Biostatistics. She conducted all the analyses of the ECRHS asthma work. She also shares the desk with Estelle Planas (PhD student) who does the SAPALDIA/ECRHS analyses in the project proposed by Jan-Paul Zock.

While CREAL should already have the full health data set of SAPALDIA 1 and 2 (needs to be checked though) CREAL may need to receive only the exposure metrics for each subject. Analyses will be initiated immediately once data are received. Preliminary results will be shared regularly in emails and telephone conferences and, possibly, meetings as needed. The current plan is to submit an abstract to ATS 2008 if ever possible.

Nino Kuenzli, Barcelona 23.7.07

ANNEX: Exposure metrics needed for each subject:

EXPOSURE METRICS NEEDED FOR THE ASTHMA INCIDENCE ANALYSES

For each SAPALDIA 2 subject included in the analyses, the following metrics are needed:

Marker	Timeframe	Year of measure (1991 & 2002)	cumulative (from 1991 to 2002)			changes (1991-2002)	max. number of exp. parameters per subject
			linear	quadratic	cubic		
PM10							
total		X	X	X	X	6	
traffic		X	X	X	X	6	
regional		X	X	X	X	6	
secondary		X	X	X	X	6	
NO2 (total)							
raw		X	X	X	X	6	
shrunk		X	X	X	X	6	
Traffic metrics (as used in Bayer-Oglesby et al)							
Distance to closest main street		X				2	
Length of main street segment, 200 m buffer		X				2	
Main street within 20 meters (Y/N)		X				2	
* PM2.5 is proportional to PM10 as was modeled, with predictions not validated due to limited measurements						42	
* central-site O3 data are available in some years.						(total)	

Note for Racquel

PROCEDURE FOR ANALYSES

1. Understand data set
2. Description of data PROC FREQ of main variables, including MOVING history variables
3. Define and describe “no asthma at baseline” and “onset of asthma” using all definitions as in Forsberg et al or Jacquemin et al.; also show year of onset of asthma among ‘new asthmatics’ to define strict and loose ‘onset’
4. Define population as non-missing information for outcome and main exposure terms
5. Describe included versus excluded population

Analyses of main hypothesis:

For Raquel

Version: 11.10.2007

1) Outcome: Asthma incidence (the various definitions)

2) Exposure variables of primary interest:

1. Pm10traff_kum
2. distmain_s1
3. main20_s1
4. length_200_s1
5. pm10reg_kum
6. pm10sec_kum

3) (apart from usual adjustment co-variates [age, sex, SES, smoking, BMI...] do with and without adjustment for

- pm10_kum
- years_sap2
- in_area

4) With and without stratification by

- In_area
- Sex
-

(NOTE: we will need the simple univariate associations of the OUTCOME with all co-variates, and of the main EXPOSURE (above #1,2,3) with the same co-variates (with p-values of chi-squares or of diff. of means)... but for the abstract we primarily need the above

OCT 30 2007: to Racquel

Notes and next steps, based on Oct 30th 2007 (submission of ATS2008 abstract)

- While we ran the above exposure metrics so far, we focused on TPM₁₀ – traffic PM₁₀ - change between S1 and S2. All these restrictions were 'prior restrictions' to prevent any fishing expeditions
- The three street/proximity/density markers did at this stage of the analysis not appear to be of much information. Cum secondary PM₁₀ did in some models/subgroups appear to be strongly associated with incidence, but not very stable story.
- We noticed that RR's are not very sensitive to the inclusion or exclusion of what we listed as candidates for confounding.
- We did, however, notice very strong indications of effect modification for factors with prior evidence/hypothesis to potentially modify the risks as well one factor not easily explained, namely MOVING STATUS.
- Effect modification reached statistical significance only for ATOPY and SMOKING (with higher RR in ATOPIC and NEVER SMOKERS), but MOVING STATUS p for interaction was often toward 0.1).
- We hypothesized the MOVING STATUS interaction being a aproxy for AGE as 'not moving' was strongly dependent on age. Age stratification did, however, not confirm this idea.

Next steps:

While we scrutinized a lot of adjustment options and interactions, the smoking interaction model was run only very lately, but appears to be for sure of relevance (as well as atopy). Thus, further analyses should now focus with scrutiny on models by smoking status. In light of the known relationship between asthma and smoking, and the complex relationship between smoking cessation and asthma, my preferred approach to the extended analyses is a focus on NEVER SMOKERS ONLY.

Do all of the following analyses in NEVER SMOKERS

1. show 3 definitions of 'asthma incidence': do all the next steps separately for THREE definitions of asthma incidence, mainly the 'loose' versus 'strict' where "strict" means: all 'new asthma' who reported a 'pre-SAPALDIA1-date of asthma onset' are considered as "asthma at baseline", thus do not qualify for the incidence analysis, and a third definition of NEW ASTHMA, where all with asthma/COPD OR with *bronchial hyperreactivity* (BHR at baseline) do also NOT qualify for the incidence population (N may be small??). Show descriptives (N) for each definition, and their cross-tabulation. All the next steps are done separately for each definition, but start with the 'strict/clear definition' used primarily so far!
2. DESCRIPTIVES: Repeat the purely bi-variate description of ALL MAIN VARIABLES AND EXPOSURE METRICS available for ASTHMATIC and NON-ASTHMATIC (using each of the above definitions, one by one) (add p-values of t-tests or chi-squares), and show the bi-variate correlations of all the main factors also with "Traffic PM₁₀ –change" (our main exposure).

3. Test main model of TPM10 in never smokers with AREA as random effect.
4. SENSITIVITY TO CONFOUNDING: Check again (in NEVER SMOKERS) the sensitivity of the RR for the various adjustment factors. Use those tested before, BUT we may need to add a few more if we find new statistically significant correlates of asthma (or of TPM10) among NEVER SMOKERS (see 2. above)
5. Repeat all INTERACTION ANALYSES as done before, but add also BHR at baseline, paternal allergies, paternal ASTHMA, Education (two classes only), baseline BMI (cut off at sex specific median).