TITLE:

Traffic-Related Air Pollution Correlates with Adult-Onset Asthma among Never-Smokers

AUTHORS:

Nino Künzli, MD PhD 1,2,3,4, Pierre-Olivier Bridevaux , MD 5, L.-J. Sally Liu, PhD 6,7 , Raquel Garcia-Esteban , MSc 1,3,4, Christian Schindler , PhD 6 , Margaret W. Gerbase , MD 5 , Jordi Sunyer , MD 1,3,4,8, Dirk Keidel MSc 6, Thierry Rochat MD 5, on behalf of SAPALDIA Team (Swiss Study on Air Pollution and Lung Diseases in Adults)

AFFILIATIONS:

1) Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
2) Catalan Institution for Research and Advanced Studies (ICREA), Spain.
3) Municipal Institute of Medical Research (IMIM), Barcelona, Spain.
4) CIBER en Epidemiología y Salud Pública (CIBERESP), Spain.
5) University Hospitals of Geneva, University of Geneva, Switzerland
6) Institute of Social and Preventive Medicine, University Basel, Switzerland
7) University of Washington, Seattle, WA, U.S.A.
8) Universitat Pompeu Fabra (UPF), Barcelona, Spain.

CORRESPONDING AUTHOR:

Nino Künzli, M.D. Ph.D.
ICREA Research Professor
Center for Research in Environmental Epidemiology (CREAL)
C. Doctor Aiguader, 88
08003 Barcelona
SPAIN
Tel.: direct (+34) 93 316 0649
FAX: (+34) 93 316 0575
Email: kuenzli@creal.cat

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ABSTRACT

BACKGROUND: Traffic-related pollution is associated with asthma onset in children. Its effect on adult-onset asthma is poorly investigated.

OBJECTIVE: We used the SAPALDIA cohort study to investigate associations between the 11-year change (1991-2002) in home outdoor traffic-related particulate matter up to 10 micrometers in diameter (TPM10) and asthma incidence.

METHODS: Never-smokers without asthma at baseline (ages: 18-60 years in 1991) were eligible. Subjects reporting doctor's diagnosed asthma at follow-up were considered incident cases. TPM10 at baseline and follow-up was predicted and interpolated to subject's residences by dispersion models using emission and meteorological data. Cox proportional hazard models for time to asthma onset were adjusted (age, gender, baseline atopy, BMI, bronchial reactivity, maternal allergies).

RESULTS: Among 2725 never-smokers, 41 reported asthma onset in 2002. Home outdoor TPM10 concentrations improved during the interval (mean: -0.6; range -9 to +7.2; IQR 0.6 $\mu g/m^3$). Asthma incidence was associated with change in TPM10. The hazard ratio (1.30; 95%CI: 1.05 – 1.61) per 1 $\mu g/m^3$ change in TPM10 (IQR) was not sensitive to further adjustments (education, workplace exposure, passive smoking, parental asthma or allergies, random area effects, lung function, or co-pollutants such as regional, secondary, total PM10, or proximity to busy roads).

CONCLUSION: The data suggest a role for traffic-related pollution in adult-onset asthma. Space, time, and source-specific individual assignment of exposure to traffic-related pollution is a key strength of SAPALDIA. It may explain why findings were statistically significant despite the limited number of new cases. As traffic-related pollution prevails, the finding may be of substantial public health relevance.

INTRODUCTION

Currently prevailing levels of ambient air pollutants exacerbate asthma. Thus, asthma-related symptoms, emergency room visits, and hospitalizations all increase, along with the need for asthma treatments, during periods with higher outdoor air pollution (1, 2). A controversial question, though, is whether chronic exposure to ambient air pollution causes new onset of asthma. Earlier studies comparing asthma prevalence across communities with different levels of pollution did not support this notion (3). However, cross-community comparisons fail to characterize contrasts in exposure occurring within communities. The main reason for such small-scale contrasts is traffic. Related pollutants reach far higher concentrations on and along busy roads as compared to locations some 50 to 200 meters away from traffic arteries (4). A recent review showed that living near traffic sources is associated with both onset and exacerbation of childhood asthma (2).

The etiology of asthma may well depend on the age of onset of the disease (5). However, adult-onset asthma has received less attention, and discussions centre mostly around smoking and occupational causes (6, 7). Cohort studies indicate that onset of asthma among adults is not uncommon; for example, the Nurses Health Study reported approximately one new case of asthma per 1,000 adults occurring every year (8). In the younger European Community Respiratory Health Survey (ECRHS), the incidence was 2.3 new cases per 1,000 person-years (9). The first study suggesting an association between home outdoor nitrogen dioxide concentrations (NO2), used as marker for traffic-related pollution, and adult-onset asthma has only recently been published (10). The suggestive results did not reach statistical significance. Most recently, ECRHS and its Nordic sister study RHINE observed very similar associations between asthma incidence and modelled NO2 concentrations (11, 12). ECHRS was based on a model with a rather limited spatial resolution (1x1km) available for the follow-up only (13, 14), while RHINE was based on air quality at baseline with no information about interval pollution.

We now use the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), a population-based cohort study initiated in 1991 and followed up 11 years later. Source-specific levels of pollution were spatially assigned to each participant and to the entire follow-up period. Recently, using this cohort, it was shown that air quality improvement is associated with attenuated lung function decline (15). The objective of this new analysis was to investigate whether individual-level change in exposure to local traffic-related pollutants correlated with adult-onset asthma. We focus the analysis on never-smokers. Tobacco smoke and ambient air pollution have hundreds of constituents in common but concentrations in cigarette smoke are much higher, thus, among smokers exposure to these constituents is dominated by smoking, a well accepted cause of asthma incidence.

METHODS

Study design and population

Selection of the study participants and methods of the cross-sectional (SAPALDIA1) and the follow-up study (SAPALDIA2) have been described elsewhere (16, 17). Random samples of adults (18-60 years) were recruited in 1990 using population registries in eight Swiss areas. Health examinations were conducted in 9,651 adults (mean age 40.6 yrs; 51% women) in 1991 (SAPALDIA1), with 8,047 participants reassessed in 2002 (SAPALDIA2). There were 5,734 participants (71.3%) without asthma or spirometry-defined chronic obstructive pulmonary disease (COPD) at baseline, and with annual home outdoor concentrations of particulate matter up to 10 micrometers in diameter (PM10) available for both surveys (Table 1 and Figure 1). The 2,725 never-smokers (47.6%) are the sample used in this analysis. Ethical approval was obtained from the Swiss Academy of Medical Sciences and the Regional Ethics Committees and via written informed consent from all participants.

Air pollution exposure assessment

We used concentrations of PM_{10} as a marker of air pollution. Details of the individual assignment of exposure are given online. In brief, the 1990 and 2000 PolluMap dispersion model was used (18). Inputs were hourly meteorological and emission inventory data (industrial and commercial construction, household heating, agricultural and forestry activities, traffic emissions) (18-20). Annual mean concentrations were derived from the hourly predictions for each 200x200 m grid cell and each source. All residential addresses were linked to the models. Values between 1990 and 2000 were interpolated using the historical trends of central-site measurements(18). We used differences in the annual traffic-related home outdoor PM_{10} concentrations between the two SAPALDIA studies to estimate the change in exposure (with a *negative change* indicating improvements in air quality). Henceforth we use the term $dTPM_{10}$ for the difference in traffic-related PM_{10} and TPM_{10} for traffic-related PM_{10}. The use of the interval exposure, defined as the cumulated mean concentration of home outdoor levels of TPM_{10} across the follow-up period, will be discussed. While our hypothesis is based on traffic-related PM_{10}, we discuss the use of change in regional, secondary, and total PM_{10} as part of the sensitivity analyses. Analyses using proximity buffers (20, 50, 75, 100, 150 meters) as markers of exposure are discussed online.

Definition of asthma and covariates

Asthma was defined as positive answers to both questions that are standard in many studies, namely "*have you ever had asthma"* and "*was this confirmed by a doctor"*(21, 22). To define onset of doctor's diagnosed asthma, henceforth referred to as "asthma," those with asthma or COPD (Forced Expiratory Volume in 1sec / Forced Vital Capacity (FEV1/FVC) <0.7) at baseline were excluded. Moreover, we excluded subjects without asthma at baseline who reported asthma at follow-up but indicated the year of onset to be prior to baseline. In sensitivity analyses, we also ignored the latter restriction, and alternatively made further restrictions at baseline, mainly requiring no asthma, no COPD, and no bronchial hyperactivity based on the standard methacholine inhalation test (22, 23).

Detailed information about current, past, and passive smoking, occupational exposure to dust and fumes, and other risk factors was gathered through interview-administered questionnaires (21). Participants were classified as atopic if they developed a wheal to one or more of the eight common inhalant allergens tested in the baseline skin-prick test (16, 21).

Statistical analysis

Details are given in the online suppository. In brief, our main goal was to determine whether changes in traffic-related air quality were associated with new onset of asthma. We focus on the associations between incidence of adult-onset asthma and $dTPM_{10}$. Models using the highly correlated TPM_{10} at SAPALDIA1 and SAPALDIA2 as well as interval exposures are discussed online.

Analyses of incidence were based on Cox proportional hazard regression models. Time to onset of asthma was measured in years from SAPALDIA1 to the reported age of first attack, or to SAPALDIA2 among those without incident asthma (in which case outcomes were treated as censored). Covariates pre-selected on prior knowledge were considered as potential confounders if associated with incident asthma at a p-value ≤ 0.2. These variables were retained in the multivariate model if p-values were < 0.1 or if the coefficient of $dTPM_{10}$ was modified by 10% or more upon their removal. For time-varying variables (BMI, BHR, FEV1) we also considered the change between SAPALDIA1 and 2 as potential confounders. Figure 2 was based on a non parametric regression using Generalized Additive Models (GAM).

Sensitivity analyses consisted of both less and more parsimonious models, and analyses were also restricted to participants who always lived in the original SAPALDIA area. We also tested

random effects of area lived in at baseline. The exploratory assessment of heterogeneity across predetermined subgroups (see Figure 3) has limited statistical power but may be of interest in comparison with future studies.

Analyses were conducted with the statistical software Stata/SE 10.0. P-values of <0.05 were interpreted as statistically significant. Proportional hazard assumptions were tested but never violated for the air pollution exposure terms.

RESULTS

Table 1 describes the main covariates of the 2,725 never-smokers without asthma or COPD at baseline, stratified by incident asthma status at follow-up. A total of 41 subjects (1.5%) developed asthma during the 11 years of follow-up, corresponding to an incidence rate of 1.39 (95% CI: 1.02 - 1.88) cases per 1,000 person-years. New cases were, on average, younger and more likely atopic at baseline than the non-asthmatic. Baseline bronchial hyperreactivity (BHR) was also more prevalent among incident cases. Non-participants are described in the online suppository and its Table S1.

TABLE 1 SEE NEXT PAGE

Traffic emissions were reduced by an average 25% across all areas between 1990 and 2000 (18). The area mean of the traffic-originated PM_{10} ranged between 0.9 and 5.4 $\mu g/m^3$ and between 0.8 and 3.1 $\mu g/m^3$ in SAPALDIA 1 and 2, respectively, accounting for between 6 and 16% of the total PM_{10} concentrations across the study areas. TPM_{10} was highly variable within areas. The within-area CV ranged from 15-36% while the spatial variation of total PM_{10} within each area was small (range of CV: 2-10%).

The distribution of area-specific $dTPM_{10}$ is presented in Figure 1. Table S4 in the online repository provides the related data for movers and non-movers. Study areas are ordered by the area mean level of TPM_{10} at baseline. Changes were largest in the more polluted areas. The overall mean $dTPM_{10}$ was -0.59 $\mu g/m^3$, with a range from -8.95 to 7.24 and an interquartile range from -0.80 to -0.21 (Table 1).

FIGURE 1

Table 1: Description of study population: lifetime never-smokers with and without incident asthma at SAPALDIA2.

	No asthma N = 2684	**New onset asthma** N = 41	**Total** N = 2725	p-value†
In % of subjects				
Age at baseline ≤40	48.55	63.41	48.77	0.059
Women	61.36	63.41	61.39	0.789
Bronchial hyperreactivity at baseline (missing, n = 506)	7.01	17.14	7.17	0.021
Atopy at baseline(missing, n = 244)	28.41	60.00	28.86	<0.001
Maternal allergies at baseline	15.22	7.50	15.10	0.176
FEV_1 at baseline ≤85% predicted	2.61	2.44	2.61	0.946
Work exposure to fumes/aerosols (at baseline)	29.65	37.50	29.76	0.281
Environmental tobacco smoke at home (at baseline)	15.09	14.63	15.08	0.936
Age ending full-time education: ≤20 yrs	66.20	65.85	66.20	0.963
Main street within 20m (SAPALDIA1 address)	18.83	17.07	18.81	0.775
Mean (S.D.)				
Age at follow-up	50.83 (12.25)	45.35 (11.58)	50.74 (12.26)	0.005
BMI at baseline	23.50 (3.65)	23.67 (3.22)	23.50 (3.64)	0.583
FEV_1 %predicted (at baseline)	123.11 (24.93)	116.17 (17.60)	123.00 (24.85)	0.120
Traffic PM_{10} at SAPALDIA 1	2.84 (1.80)	2.42 (1.61)	2.84 (1.80)	0.120
Traffic PM_{10} at SAPALDIA 2	2.25 (1.43)	2.17 (1.43)	2.25 (1.43)	0.126
Total PM_{10} at SAPALDIA 1	27.68 (10.03)	26.46 (10.32)	27.66 (10.04)	0.393
Total PM_{10} at SAPALDIA 2	21.45 (7.17)	21.41 (7.90)	21.45 (7.18)	0.440
Change in total PM10	-6.23 (4.40)	-5.05 (5.02)	-6.21 (4.41)	0.619
Change in traffic PM_{10} (µg/m^3) (main exposure metric)	**-0.59 (1.13)**	**-0.25 (1.40)**	**-0.59 (1.14)**	
25th percentile	-0.80	-0.61	-0.80	--
50th percentile	-0.39	-0.30	-0.39	--
75th percentile	-0.21	-0.11	-0.21	--
Interquartile range (IQR)	0.59	0.50	0.59	--

† p-value for chi-squared or Kruskal-Wallis test comparing the two groups

Table 2 reports the asthma incidence hazard ratios for a 1 μg/m^3 change (approximately IQR) in TPM_{10} from several models. The hazard ratios were not sensitive to modelling assumptions. We observed a tendency toward stronger associations in multivariate models as compared to the unadjusted model or the age- and sex-adjusted basic model (see Table 2).

TABLE 2 SEE NEXT PAGE

Adjustment for area or the number of years lived at the baseline address did not affect the point estimates either. A stricter definition of "no asthma", excluding subjects with hyper-reactive airways at baseline, reduced the population to 1,846 subjects. However, associations with $dTPM_{10}$ remained similar (HR=1.27 [95% CI: 1.01 -1.61] per μg/m^3 dTPM10). As shown in Table 3, adjustment for change in regional, secondary, or total PM_{10} did not affect the point estimates for dTPM10 but inflated the confidence intervals yielding non-significant estiamtes. Hazard ratios of the 11-year change in these co-pollutants were instead very sensitive to adjustment by dTPM10. The null findings among smokers are shown in Table S2 in the online supplement.

TABLE 3 SEE NEXT PAGE

Residential proximity to busy roads was not associated with asthma. These results are discussed in the online suppository (including Table S3).

Figure 2 shows the association between $dTPM_{10}$ and the log of the hazard ratio based on the main model of Table 2.

FIGURE 2

Area-specific estimates of $dTPM_{10}$ reached statistical significance in only two communities (Wald and Payerne), with no indication of heterogeneity of associations across areas (p=0.3). Hazard ratios among the subgroups explored for interaction are presented in Figure 3. None of the apparent differences reached statistical significance for effect modification. Associations of $dTPM_{10}$ with asthma onset appeared larger among those with parental allergies (p for heterogeneity: 0.088). In general, estimates were larger among non-movers with the main model HR reaching 1.53 (1.02-2.28).

Table 2: Association between change in traffic-originated PM_{10} and asthma incidence among SAPALDIA never-smokers. Hazard ratios (HR) are given per 1 µg/m^3 dTPM10, and presented for several models. The first 2 models include all 41 new cases of asthma; the others are based on 38 new cases due to some missing data in the co-variates.

	N	HR	(95% C.I.)	p-value
Unadjusted association	2725	1.28	(1.01 - 1.61)	0.040
Adjusted for:				
- Age, gender	2725	1.22	(0.98 - 1.51)	0.072
- Age, gender, baseline atopy, BMI, bronchial hyperreactivity, maternal allergies (**Main model**)	2390	1.30	(1.05 - 1.61)	0.018
- Main model + paternal asthma	2303	1.34	(1.08 - 1.67)	0.007
- Main model + random effect for study area	2390	1.32	(1.06 - 1.65)	0.013
- Main model + education and work exposure	2368	1.30	(1.05 - 1.61)	0.018
- Main model + FEV_1 at baseline (% predicted)	2390	1.30	(1.05 - 1.61)	0.015
- Main model + Environmental tobacco smoke at baseline	2390	1.30	(1.05 - 1.61)	0.018
- Main model + years lived at SAPALDIA2 address	2380	1.30	(1.03 - 1.63)	0.025
Main model, Non-movers only (same residence SAPALDIA 1 and 2)	2022	1.53	(1.02 - 2.28)	0.039
Main model, but loose definition of "new asthma" 1)	2409	1.17	(0.96 - 1.42)	0.114

1) Includes newly reported asthma at SAPALDIA2 but age of onset reported as before SAPALDIA 1; age of onset was set to 0.1yrs

Table 3: Association between PM_{10} (change in traffic-related, regional, secondary, and total PM10, and level at SAPALDIA 1) and asthma incidence among SAPALDIA never-smokers. Hazard ratios (HR) and 95%CI are given per 1 µg/m^3 and based on single-pollutant and two-pollutant models, adjusted for age, gender, baseline atopy, BMI, bronchial hyperreactivity, maternal allergies (main model of Table 2). All models include 2,390 subjects and 34 new cases of asthma. "Total PM10" is the sum of all PM10, and thus includes traffic-related PM10.

Exposure metric	Single-pollutant Model		Two-pollutant model			
			HR for dTPM10		HR for co-pollutant	
Change in traffic-related PM_{10} (dTPM10)	1.30	(1.05 - 1.61)	1.30	(1.05 - 1.61)	N/A	
Change in regional PM10	1.10	(0.94 - 1.30)	1.28	(1.00 - 1.64)	1.02	(0.86 - 1.21)
Change in secondary PM10	1.44	(0.89 - 2.33)	1.30	(0.98 - 1.71)	1.00	(0.53 - 1.92)
Change in total PM10	1.07	(1.00 - 1.14)	1.22	(0.88 - 1.71)	1.02	(0.93 - 1.13)
Level of traffic-related PM10 at SAPALDIA 1	0.80	(0.64 - 1.00)	1.22	(0.93 - 1.59)	0.87	(0.68 - 1.11)

DISCUSSION

This study suggests a role of traffic-related air pollution in the development of adult-onset asthma among never-smokers. These results are in line with numerous studies conducted in children. According to a recent review by Salam et al., evidence for a causal role of traffic-related air pollution on childhood asthma onset is strong (2) and more recent studies further support the conclusions of Salam et al (24). The available individually assigned long-term characterization of home outdoor pollution offered the unique opportunity to investigate how the change in traffic-related air quality affected adult-onset asthma. SAPALDIA has previously shown that improvement in air quality is associated with an attenuation in the decline of pulmonary function (15). Our novel results suggest that a decrease in air pollution is also paralleled by a reduced risk to develop asthma as an adult – or an increase in pollution correlates with a larger number of adult onset asthma. The results need to be put in context of several strengths and limitations. We first address challenges related to air pollution exposure assessment and then discuss the interpretation of the health outcome.

We believe that our ability of space, time, and source-specific assignments of individual exposure is not only a strength, but most likely a *condition* to investigate the asthma onset hypothesis successfully. Our primary exposure term was the change in traffic-originated PM10. Air quality improved during follow-up, but more so in the more polluted areas, leading to a negative correlation between baseline TPM_{10} and its change (dTPM10) (r= -0.76). Interval exposure correlated negatively with the change in TPM_{10} as well (r=-0.59). Thus, neither baseline exposure nor air quality at follow-up or interval exposure would capture the dynamic of subject's exposure history. The only adequate alternative approach to our analysis would consist of the use of the interval exposure with adjustment for baseline TPM10, which corresponds conceptually and mathematically to our use of the *change* in TPM10. While this strategy gave similar point estimates (Table 3), the collinearity between baseline TPM_{10} and interval TPM_{10} greatly reduces precision in the estimation, underscoring the advantage of temporally resolved individual assignment of change in exposures.

The needs for accurate *spatial* and *source-specific* assignment of exposure are interrelated challenges for a successful investigation of the asthma hypothesis. Contrasts in subjects' exposure to air pollutants originate to a large extent from spatial heterogeneity in air quality *within cities*. These contrasts are primarily driven by traffic-originated pollutants, which can easily increase 5 to10 times in concentration along the traffic arteries while decreasing to "urban-background" concentrations within 200 meters of such roads (4, 25). Thus, it is important to identify the exact residential location, and to model traffic-specific markers of air pollution that reflect local spatial patterns. Our outdoor exposure model used source-specific emission inventories and estimated concentrations with a spatial resolution of 200x200 meters (18). Models of some tail-pipe constituents may be improved with higher resolution. In this case, our estimates are likely to be biased to the null. Like other studies, we also ignored time at work or in commute. This misclassification may attenuate estimates but we expect little bias as home outdoor remains the most important determinant of personal exposure to pollutants from outdoor origin (26).

TPM_{10} ought to be considered a proxy for traffic-related primary pollutants rather than the culprit pollutant *per se*. Spatial distributions of other biologically relevant traffic-related toxicants (such as PM2.5, ultrafine particles, polycyclic aromatic hydrocarbons (PAH's), or redox active metals contained on fine PM) were not modelled separately and their correlation with TPM_{10} is not known. It may, however, be that what we label as "TPM10" to partly capture the spatial distribution in the exposure to ultrafine particles or other traffic-related constituents. Other markers of local traffic-related pollutants or PM compositions may result in different effect scales.

In contrast to several studies conducted in children, residential proximity to busy roads was not associated with asthma onset in our study. The limitation of such markers in a longitudinal study are discussed in the online suppository.

Point estimates were higher among subjects with better exposure assessment, namely those who never moved. Associations of asthma onset with PM_{10} from other sources were not only smaller but substantially decreased with adjustment for traffic-related PM_{10} (e.g. PM10 at baseline in Table 3; other data not shown). In line with the findings in children, this observation further underscores the relevance of traffic-related versus urban background pollution in asthma development.

As emphasized by Eder et al., asthma is a syndrome rather than *one* disease, and various phenotypes of "asthma" may have different risk patterns (1). Our abilities to specify asthma phenotypes were limited as we relied on reported 'doctor's diagnosed asthma' as used in many epidemiological studies. This precludes a more detailed assessment of phenotypes and the clinical distinction between asthma and COPD. The latter were excluded from our baseline population, and the analyses are restricted to non-smokers, thus, the impact of misclassified diagnoses may be rather marginal in this analysis.

However, a major related problem is the definition of 'onset of asthma'. The distribution of time to onset varied substantially (online Tables S5), and many reported onset of asthma prior to SAPALDIA 1 but did not report asthma at baseline. If we include those 'loosely defined' new cases of asthma, associations remained positive but no longer statistically significant (see online Table S6). Given the uncertainties related to the time-of-onset, the change in TPM10 was derived as the difference between SAPALDIA 1 and 2. The - in theory - more appealing definition of exposure windows until *asthma onset* is discussed online. These attenuated and non-significant findings must be interpreted with caution.

The identification of susceptible subgroups is of both public health and biologic relevance. Given the limited number of new cases, we can only speculate about the meaning of the patterns shown in Figure 3. Taken at face value, the results would indicate that those with an inherently higher baseline risk for asthma due to atopy, BHR, or parental asthma are more strongly affected by traffic-originated pollution. However, none of the interactions was statistically significant, which may reflect random variation. Modig et al. reported higher risks among atopics [10].

Onset of asthma among smokers – another group with inherently higher asthma incidence – was not associated with TPM10 (see Table S2 in the online supplement). If similar combustion-related constituents and immunologic mechanisms were involved in asthma onset due to both, smoking and traffic-relate pollution, the contribution of the latter exposure may be marginal among smokers, resulting in null findings for TPM10.

Modig et al. was the first study using a marker of local traffic-related pollution, namely NO2, to investigate the asthma onset hypothesis in adults. While findings are in line with our results, correlations were not statistically significant in this Swedish case-control study (N=2x203) [10]. It is also of note that traffic-related PM_{10} at SAPALDIA2 was not associated with asthma onset. Since the Swedish study was based on cases and controls recruited from only one city (77,000 inhabitants), the subjects may all have experienced the same (unknown) temporal trends in exposure. Therefore, one may expect that "current exposure" adequately ranked people's current, past, as well as cumulative exposure. This assumption does not hold for SAPALDIA, which may explain the discrepancy between our results and those from the first Swedish study. In ECRHS, asthma incidence also correlated significantly with home outdoor NO2 concentrations at follow-up, derived from an emission based model (11). As in the first Swedish study, assignment of traffic-related exposure was done only for the address at follow-up as

baseline air quality data were not available (13), thus, the positive results contrast with the null findings seen in our study if exposure at SAPALDIA2 was used. It is not known whether air quality changes followed similar patterns for all participants across the 21 ECRHS centres, but follow-up in ECRHS was on average a few years shorter. The most recent Swedish study (2009) reported strikingly similar results as ECRHS, but was based on an NO2 dispersion model of high resolution (50x50m) (12). Our use of TPM10 precludes a quantitative comparison of risk estimates. Again in contrast to our study, the Swedish study defines baseline exposure only. Spatial contrasts and changes may be less correlated in this study with shorter follow-up (8.3 yrs) and only three urban areas.

While the Seventh Day Adventist study (AHSMOG) reported an association between asthma incidence and ozone in men, as well as non-significant associations with particulate matter during the follow-up initiated in the late 1970s, local traffic-related pollution was not characterized [(22)(21)]. Time, location, and population characteristics substantially differ between AHSMOG and SAPALDIA, limiting formal comparisons.

Biases are not a plausible explanation for our positive findings. Point estimates were neither sensitive to model specification nor to adjustment for fixed and time-varying determinants of asthma incidence nor study area (fixed or random effect). It appears unlikely that some uncontrolled factor was a strong enough risk for asthma onset *and* sufficiently correlated with $dTPM_{10}$ to confound our estimates. To avoid multiple comparisons we *a priori* restricted the main analyses on one single marker of exposure, namely traffic-related particles. Despite small numbers of new cases, associations were clearly statistically significant in several models, and thus are unlikely explained by chance alone.

The consistency between our findings and observations made in children suggests that similar mechanisms may be involved both in early-life asthma and adult-onset asthma. Many of the traffic-originated pollutants have strong redox cycling capacity (27-29). This results in oxidative stress and both local as well as systemic inflammation, which are considered key pathways in the development of asthma (27, 30). Experimental studies confirm an adverse role in IgE mediated allergic responses which may play a role in asthma development among atopic subjects (31). Our data suggest the latter to be more strongly affected by traffic-related pollution. Respective findings among children are not consistent (2). This inconsistency may suggest different pathways being involved in childhood and adult-onset asthma among those exposed to traffic-related pollution. Future studies on adult-onset asthma may investigate the interaction of traffic-originated pollutants with genetic variants to elucidate the mechanisms involved in the observed associations.

In summary, the ability to assign space, time, and source-specific exposure to traffic-related pollution to each individual is a strong feature of SAPALDIA. In line with numerous studies conducted in children, the findings suggest that traffic-related local pollutants contribute to asthma development, and even more importantly that reductions in these pollutants decrease asthma risks as well. Given the widespread exposure to traffic pollution, we recommend studies to investigate the mechanisms of adult-onset asthma, and identify the most susceptible subjects. Studies with much larger sample size of asthma cases would greatly attenuate all limitations faced in this study.

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Study directorate: T Rochat (p), U Ackermann-Liebrich (e), JM Gaspoz (c), P Leuenberger (p), LJS Liu (exp), NM Probst Hensch (e/g), C Schindler (s).
Scientific team: JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), G Bolognini (p), O Brändli (p), M Brutsche (p), L Burdet (p), M Frey (p), MW Gerbase (p), D Gold (e/c/p), W Karrer (p), R Keller (p), B Knöpfli (p), N Künzli (e/exp), U Neu (exp), L Nicod (p), M Pons (p), E Russi (p), P Schmid-Grendelmeyer (a), J Schwartz (e), P Straehl (exp), JM Tschopp (p), A von Eckardstein (cc), JP Zellweger (p), E Zemp Stutz (e).
Scientific team at coordinating centers: PO Bridevaux (p), I Curjuric (e), SH Downs (e/s), D Felber Dietrich (c), A Gemperli (s), D Keidel (s), M Imboden (g).
(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (p) pneumology, (s) statistics.

LEGENDS TO FIGURES

Figure 1: Distribution of the change in traffic-related individually assigned PM_{10} by study area and for the total sample. The eight areas are ordered by the annual mean TPM_{10} at baseline. Negative changes mean improvements in air quality. The reduction in TPM_{10} was on average larger in the most polluted areas (Basel and Geneva). Boxes show the median and quartiles (25^{th} and 75^{th} percentile) of the distribution.

Figure 2: Association between change in traffic-related PM_{10} and adult-onset asthma (log-hazard with 95%-confidence interval) among SAPALDIA never-smokers. (Generalized additive model, adjusted for age, sex, atopy at baseline, BMI at baseline, bronchial hyperreactivity at baseline, maternal allergies.) The symbols (+) on the X-axis indicate observations.

Figure 3: Association between incidence of asthma and change in traffic-related PM_{10} among subgroups of never-smokers (models are adjusted for age, sex, atopy at baseline, BMI at baseline, bronchial hyperreactivity at baseline, maternal allergies). Hazard ratios are presented per 1 $\mu g/m^3$ dTPM10 with 95% CI (p-value for interaction for parental allergies = 0.088; all other interactions p>0.1).

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Figure 1: Distribution of the change in traffic-related individually assigned PM_{10} by study area and for the total sample. The eight areas are ordered by the annual mean TPM_{10} at baseline. Negative changes mean improvements in air quality. The reduction in TPM_{10} was on average larger in the most polluted areas (Basel and Geneva). Boxes show the median and quartiles (25th and 75th percentile) of the distribution.

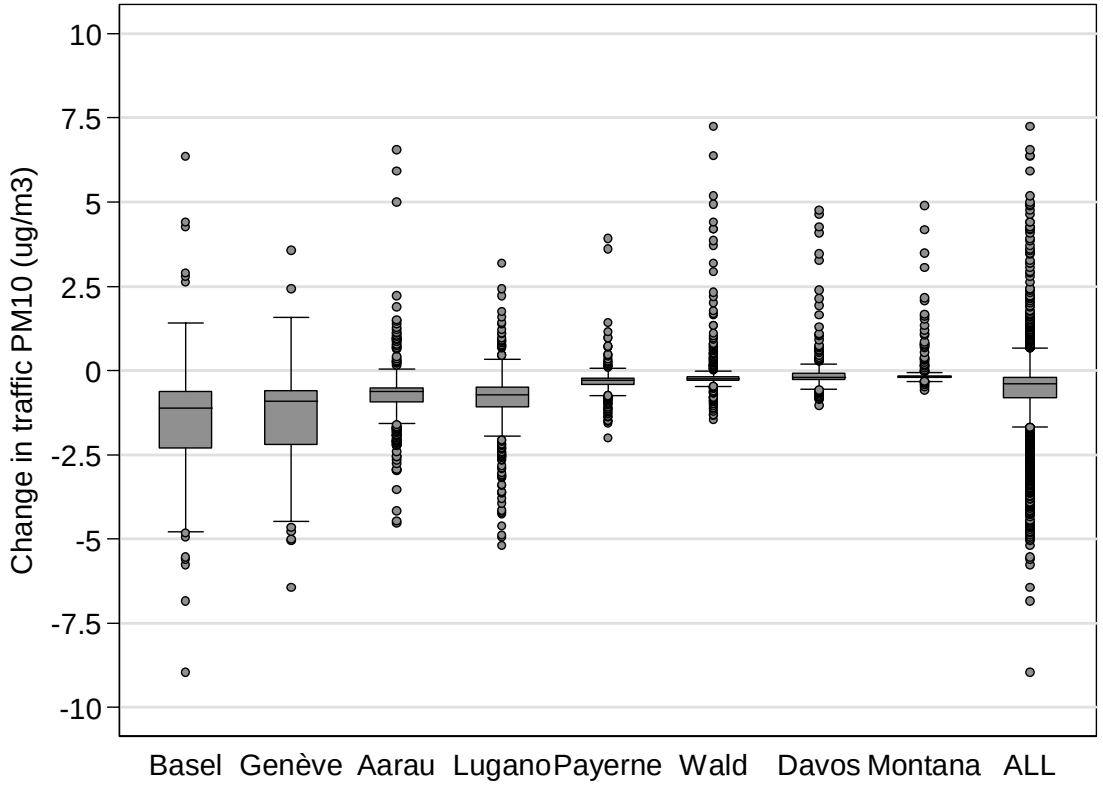


Figure 2: Association between change in traffic-related PM_{10} and adult-onset asthma (log-hazard with 95%-confidence interval) among SAPALDIA never-smokers. (Generalized additive model, adjusted for age, sex, atopy at baseline, BMI at baseline, bronchial hyperreactivity at baseline, maternal allergies.) The symbols (+) on the X-axis indicate observations.

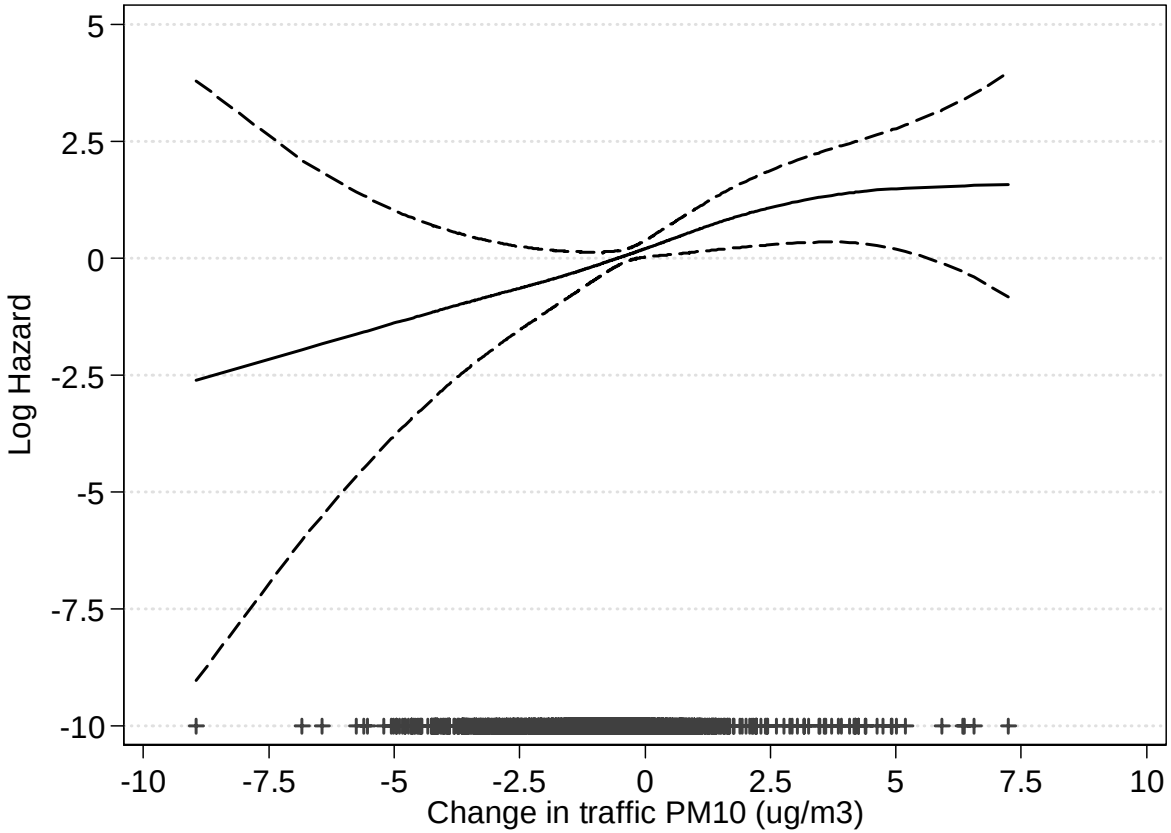
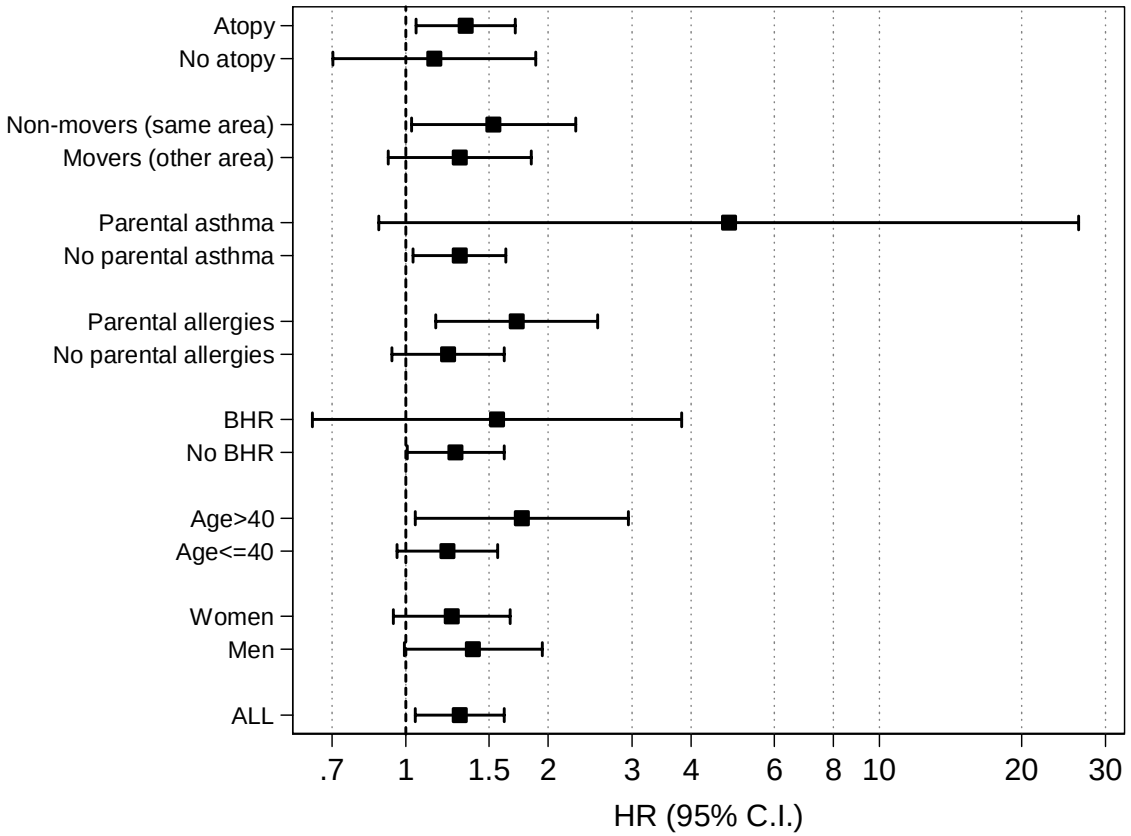


Figure 3: **Association between incidence of asthma and change in traffic-related PM_{10} among subgroups of never-smokers (models are adjusted for age, sex, atopy at baseline, BMI at baseline, bronchial hyperreactivity at baseline, maternal allergies). Hazard ratios are presented per 1 µg/m^3 dTPM10 with 95% CI (p-value for interaction for parental allergies = 0.088; all other interactions p>0.1).**



ONLINE REPOSITORY

Air pollution exposure assessment

We used concentrations of PM_{10} as a marker of air pollution. Individual exposure was estimated using the PolluMap dispersion model (18). The inputs to the models included hourly meteorological and emission inventory data in 1990 and 2000 on industrial and commercial construction, household heating, agricultural and forestry activities, and traffic emissions (18-20). Traffic emissions were computed for the road network for passenger cars, light-duty vehicles, motorcycles, and buses. Emissions from heavy-duty vehicles were computed separately from an update road network and a new relative distribution of traffic loads (18). Emission strength was modelled for diurnal variation, weekday-weekend differences, and seasonal variation due to heating and photochemical reactions. Hourly predictions for each source were averaged over the year to obtain annual averages for each 200x200 m grid cell. All residential addresses of all participants were geo-coded and assigned to an annual concentration after matching the address codes with the concentration grid cells generated by the dispersion model for 1990 and 2000, respectively. We then developed an algorithm to interpolate dispersion modeled values between 1990 and 2000 using the historical trends of central-site measurements(18). The historical trends were assessed within defined areas with comparable sources or climatic characteristics, including the catchment areas of the eight study centers and the regions of Zurich and Bern. Each area was represented by at least one monitoring station. Addresses outside these areas were grouped into four "other" areas based on similarities in meteorology and pollution sources. Our comparisons of measured and modelled variations within and between cities indicated that the modelled variations were consistent with measured values both within and between cities(18). We used differences in the annual traffic-related home outdoor PM_{10} concentrations between the two SAPALDIA studies to estimate the change in exposure (with a *negative change* indicating improvements in air quality). Henceforth we use the term $dTPM_{10}$ for the difference in traffic-related PM_{10} and TPM_{10} for traffic-related PM_{10}. The use of the interval exposure, defined as the cumulated mean concentration of home outdoor levels of TPM_{10} across the follow-up period, will be discussed. As examined in detail by Liu et al, the emission-based models allowed the derivation of various types of PM_{10} (18). While our hypothesis is based on traffic-related PM_{10}, we discuss the use of change in regional, secondary, and total PM_{10} as part of the sensitivity analyses based both on single-pollutant and two-pollutant models. For comparison with other approaches, we present results for analyses using various proximity buffers (20, 50, 75, 100, 150 meters) as markers of exposure.

Statistical analysis

Our main goal was to determine whether changes in traffic-related air quality were associated with new onset of asthma. Individual levels of exposure at baseline were negatively correlated with change as air quality improved, primarily in the most polluted areas. Moreover, individual interval exposures and change in exposure were negatively correlated as well, limiting the ability to model effects of two exposure metrics in one model, e.g. interval exposure with adjustment for baseline levels. Thus, we focus on the associations between incidence of adult-onset asthma and $dTPM_{10,}$ but we will also discuss models using TPM_{10} at SAPALDIA1 and SAPALDIA2 as well as the interval exposure.

Analyses of incidence were based on Cox proportional hazard regression models. Time to onset of asthma was measured in years from SAPALDIA1 to the reported age of first attack, or to SAPALDIA2 among those without incident asthma (in which case outcomes were treated as censored). Covariates preselected on prior knowledge were considered as potential confounders if associated with incident asthma at a p-value ≤ 0.2. These variables were retained in the multivariate model if p-values were < 0.1 or if the coefficient of $dTPM_{10}$ was modified by 10% or more upon their removal. For time-varying variables (BMI, BHR, FEV1) we also considered the change between SAPALDIA1 and 2 in these factors as potential confounders.

The association between asthma onset and air pollution was also assessed with a non parametric regression using Generalized Additive Models (GAM). Each component of the resulting estimated non-parametric function of covariates is a (cubic) smoothing spline. The GAM result is illustrated in Figure 2.

Sensitivity analyses consisted of both less and more parsimonious models, and analyses were also restricted to participants who always lived in the original SAPALDIA area. We also tested random effects of area lived in at baseline. The exploratory assessment of heterogeneity across predetermined subgroups (see Figure 3) may be of interest in comparison with future studies but precludes conclusive interpretation due to the limited number of new cases.

Analyses were conducted with the statistical software Stata/SE 10.0. P-values of <0.05 were interpreted as statistically significant. Proportional hazard assumptions were tested but never violated for the air pollution exposure terms.

Subjects excluded from the analysis

In line with the inclusion criteria, subjects excluded (N=68) from the analyses were more likely to be asthmatic, to have low FEV1, and increased BHR at baseline. Men and older subjects were also less likely to be included in this analysis, and 32 were excluded due to missing dTPM10 data. All other factors shown in Table 1 did not differ among participants and non-participants (see Table S1). Asthmatics excluded from the analysis (N=35) had missing information on age of onset (N=10) or reported onset prior to SAPALDIA 1 (N=25).

Proximity to busy roads and asthma incidence

Neither in all nor in the non-movers was living in proximity to busy roads (20, 50, 75, 100, 150m within a highway or class 1 road of at least 6m width) associated with asthma onset. Estimates for dTPM10 were not sensitive to co-adjustment for distance (see Table S3 in the online supplement).
This negative finding contrasts to several studies conducted in children and the recent Swedish analysis (12). Proximity ignores a range of important determinants of local concentrations that were included in our dispersion model, such as car density, truck traffic density, meterology, urban structure, or day of the week, to name a few (18). The complex pattern of change in the individual exposure observed in our study highlights the limitations of these simpler proxies of exposure assessment if applied to longitudinal data. As time passes, (true) exposure related to living along traffic arteries ('proximity') may substantially change both in composition and concentration as car fleets, prevailing engine technology, and fuel formulas change. These qualitative and quantitative changes are not captured at all with 'proximity'. In fact, a comparison of dTPM10 among non-movers reveals significantly larger reductions between SAPALDIA 1 and 2 for those living along the traffic arteries as compared to those living further away (data not shown). This underscores the limitation of 'proximity' as a marker of pollution in a longitudinal study. Moreover, among movers, the derivation of a valid proximity-based '*change in exposure*' is rather impossible.

The recent Swedish 3-city study reported significant associations of proximity with asthma onset in adults. The Swedish study had a shorter follow-up (8.3 years) and we do not know whether and how traffic-related air quality changed (along busy roads) during these years. Moreover, a positive answer to the doctor's confirmation of asthma was not required in the definition of onset. Thus, 'incidence' was higher and may include adults labelling their respiratory symptoms as 'asthma'. Other (or additional) pollutants may be involved in triggering symptoms than those causing asthma onset, and it is not clear how the Swedish pollution space – as defined by proximity alone – may relate to these pollutants. The dispersion model based results of the Swedish study were fully consistent with our pollutant based

findings. Quantitative comparison is not possible though due to the use of different markers, namely NO2 and TPM10.

Define exposure window until time of onset only.

Given the uncertainties related to the time-of-onset, both in new cases and non-asthmatics (see main paper discussion), the change in TPM10 was derived as the difference between SAPALDIA 1 and SAPALDIA 2. In an alternative approach applied to asthma cases, change in exposure was defined as the difference between SAPALDIA 1 and the reported time of asthma onset. The distribution of time-to-onset is shown in Table S5. As shown in Tables S6, estimates were attenuated and not statistically significant in models based on this alternative definition of the exposure window.

Misclassification of 'time of onset' is likely to be substantial as it heavily depends on the doctor's diagnostic and disease labelling attitudes, and the recall of participants, which in turn may depend on the severity of the disease. Due to the small sample size within areas, it is not possible to conduct a formal comparison of the time of onset across areas. Mean time to onset shown in Table S5 ranged, however, from 2 to 6 years, and the maximum ranged from 3 to 10 years, across areas, indicating indeed regional differences, which may to some extent be a proxy for differences in diagnostic attitudes. Although we have no data to proof, one may indeed argue that labelling attitudes possibly be different in areas where health services are dominated by general practitioners (such as the more rural – and cleaner – SAPALDIA areas), as compared to areas with University Hospitals and/or pneumology centres, e.g. the – more polluted – city of Basel or Geneva.

Moreover, the restriction to the shorter exposure window results in smaller changes (i.e. reduced dTPM10) which affect the confidence intervals of the estimates.

In summary, the theoretically more appealing restriction of the exposure window to the time of onset comes with a range of inherent and possibly severe methodological problems, requiring a cautious interpretation of the related attenuated and non-significant findings.

TABLE S1: Comparison of main co-variates among those included (participants) and not included (non-participants) in this analysis (never-smokers only)

Co-variate	Non-participants N = 68		Participants N = 2725		p-value
n (%) of subjects					
Non-asthmatics	31	(46.97)	2684	(98.50)	
Asthmatic cases	35	(53.03)	41	(1.50)	<0.001
Age at baseline ≤40	41	(60.29)	1329	(48.77)	
Age at baseline > 40	27	(39.71)	1396	(51.23)	0.060
Men	20	(29.41)	1052	(38.61)	
Women	48	(70.59)	1673	(61.39)	0.124
No BHR at baseline	51	(75.00)	2060	(75.60)	
BHR at baseline	7	(10.29)	159	(5.83)	
BHR at baseline missing	10	(14.71)	506	(18.57)	0.245
No atopy at baseline	23	(42.59)	1765	(71.14)	
Atopy at baseline	31	(57.41)	716	(28.86)	<0.001
No maternal allergies at baseline	57	(87.69)	2226	(84.90)	
Maternal allegies at baseline	8	(12.31)	396	(15.10)	0.725
No paternal allergies at baseline	57	(87.69)	2320	(90.38)	
Paternal allegies at baseline	8	(12.31)	247	(9.62)	0.402
No maternal asthma at baseline	58	(87.88)	2556	(96.02)	
Maternal asthma at baseline	8	(12.12)	106	(3.98)	0.005
No paternal asthma at baseline	57	(87.69)	2474	(95.15)	
Paternal asthma at baseline	8	(12.31)	126	(4.85)	0.015
FEV_1 at baseline >85% predicted	67	(98.53)	2654	(97.39)	
FEV_1 at baseline ≤85% predicted	1	(1.47)	71	(2.61)	-
No work exposure to fumes/aerosols	54	(79.41)	1909	(70.24)	
Work exposure to fumes/aerosols	14	(20.59)	809	(29.76)	0.101
No ETS at home (at baseline)	58	(85.29)	2314	(84.92)	
ETS at home	10	(14.71)	411	(15.08)	0.932
Education: > 20 yrs	23	(35.94)	913	(33.80)	
Education: ≤20 yrs	41	(64.06)	1788	(66.20)	0.721
Movers (other area)	9	(23.68)	422	(15.50)	
Non-movers (same area)	29	(76.32)	2301	(84.50)	0.176
No main street within 20m (SAP1 address)	42	(75.00)	2206	(81.19)	
Main street within 20m	14	(25.00)	511	(18.81)	0.242
Mean (S.D.)					
Age at follow-up	48.52	(13.43)	50.74	(12.26)	0.153
BMI at baseline	23.48	(3.52)	23.50	(3.64)	0.985
FEV_1 %predicted (at baseline)	120.27	(22.45)	123.00	(24.85)	0.407
Traffic PM10 at SAPALDIA 1	3.72	(1.90)	2.84	(1.80)	0.004
Traffic PM10 at SAPALDIA 2	2.55	(1.47)	2.25	(1.43)	0.178
Change in traffic PM10	-1.17	(1.50)	-0.59	(1.14)	0.041
Total PM10 at SAPALDIA 1	29.27	(8.66)	27.66	(10.04)	0.120
Total PM10 at SAPALDIA 2	22.85	(5.99)	21.45	(7.18)	0.178
Change in total PM10 (microgr/m^3)	-6.42	(3.66)	-6.21	(4.41)	0.267

p-value for chi-square or Fisher exact test (categorical) and kruskal-wallis (continuous) comparing the two groups.

N=36 for descriptives of air pollutants among non-participants

TABLE S2: Association (Hazard Ratios and 95% confidence intervals) between change in traffic-related PM10 between SAPALDIA 1 and 2 (dTPM10) and asthma onset in "ever smokers". Results are shown for seven different models, including the main model presented for never-smokers (model 3).

Model specification	N	HR	(95% C.I.)	p-value
1. Crude	1251	0.95	(0.61 - 1.48)	0.808
Adjusted for:				
2. Age, and gender	1251	0.97	(0.63 - 1.50)	0.888
3. #2 + maternal allergies, atopy, BMI at baseline, and BHR	1096	0.99	(0.64 - 1.53)	0.968
4. #3 + paternal asthma	1052	0.99	(0.63 - 1.56)	0.961
5. #3 + AREA random effect	1096	0.99	(0.64 - 1.53)	0.964
6. #3 + education, smoking, and work exposure	1080	0.97	(0.63 - 1.50)	0.885
7. #3 + packyears (between SAPALDIA 1 and SAPALDIA 2)	955	1.00	(0.66 - 1.53)	0.993

TABLE S3: Association (Hazard Ratios and 95% confidence intervals) between alternative markers of traffic related pollution and asthma onset among never smokers who lived at the same residence both in SAPALDIA 1 and 2 (N=2022). Results are based on the main model defined in Table 2 and also used in Table 3 of the manuscript (i.e. adjusted for age, gender, baseline atopy, BMI, bronchial hyperreactivity, maternal allergies).

Exposure metric		HR	(95% C.I.)
Living within 20m of a main road		1.24	(0.50 - 3.08)
Living within 50m of a main road		1.17	(0.55 - 2.49)
Living within 75m of a main road		0.69	(0.33 - 1.48)
Living within 100m of a main road		0.73	(0.34 - 1.57)
Living within 150m of a main road		0.87	(0.35 - 2.16)
Length of streets within a 200m buffer (residence) (HR per 10m)		0.99	(0.98- 1.01)
Main effect for dTPM10:	Main model only (same as Table 2, non-movers, in main manuscript)	1.53	(1.02- 2.28)
	Main model plus adjustment for 'Traffic PM10 at SAPALDIA 1'	1.45	(0.90- 2.34)
	Main model plus adjustment for 'living within 20m of a main road'	1.53	(1.03- 2.28)

TABLE S4: Distribution of change in traffic-related PM10 by SAPALDIA area, presented for movers and non-movers.

	ALL	Movers									Non-movers								
		ALL	Basel	Wald	Davos	Lugano	Montana	Payerne	Aarau	Genève	ALL	Basel	Wald	Davos	Lugano	Montana	Payerne	Aarau	Genève
N	2725	422	53	104	49	40	23	54	80	19	2301	276	457	168	398	231	280	295	196
Mean	-0.588	-0.403	-2.504	0.636	0.746	-0.972	1.105	-0.237	-0.742	-2.856	-0.623	-1.228	-0.263	-0.218	-0.887	-0.145	-0.335	-0.698	-1.283
S.D.	1.14	1.96	1.69	1.57	1.47	1.44	1.50	1.04	1.87	1.71	0.90	1.51	0.21	0.21	0.94	0.27	0.27	0.58	1.36
Min	-8.947	-6.437	-5.761	-1.471	-1.039	-4.616	-0.296	-2.011	-4.547	-6.437	-8.947	-8.947	-1.318	-0.845	-5.204	-0.572	-1.570	-3.536	-5.008
P_5	-2.786	-3.642	-4.954	-0.639	-0.781	-3.642	-0.263	-1.355	-2.970	-6.437	-2.457	-3.974	-0.536	-0.604	-3.042	-0.303	-0.835	-1.931	-4.047
P_{25}	-0.797	-1.325	-3.555	-0.269	-0.193	-1.903	-0.071	-0.747	-1.728	-4.140	-0.762	-1.629	-0.299	-0.278	-1.054	-0.226	-0.383	-0.762	-1.712
P_{50}	-0.387	-0.323	-2.840	0.136	0.350	-0.680	0.692	-0.521	-1.192	-2.901	-0.391	-0.980	-0.251	-0.207	-0.731	-0.192	-0.280	-0.606	-0.851
P_{75}	-0.207	0.423	-1.452	0.751	1.027	-0.200	1.666	0.016	-0.111	-1.986	-0.222	-0.608	-0.208	-0.135	-0.507	-0.164	-0.236	-0.527	-0.580
P_{95}	0.705	3.462	0.134	4.199	4.255	0.788	4.171	1.405	2.058	1.373	0.133	0.732	0.038	0.041	0.337	0.173	-0.059	0.216	0.489
Max	7.240	7.240	2.774	7.240	4.751	3.175	4.907	3.919	6.557	1.373	6.340	6.340	0.765	1.059	2.431	2.081	0.710	1.262	3.577

TABLE S5: Distribution of time to asthma onset (years from SAPALDIA1 to onset as reported at SAPALDIA2) among the 41 new cases of asthma.

Group	N	Mean	S.D.	Min	P_{25}	P_{50}	P_{75}	Max
ALL	41	4.77	(3.09)	0.40	4.33	7.16	9.93	10.23
Movers	10	4.88	(2.97)	0.84	5.24	7.16	8.90	8.90
Non-movers	31	4.74	(3.17)	0.38	3.83	7.33	10.17	10.23

TABLE S6: Association between change in traffic-related modelled PM10 (dTPM10) and asthma onset among never-smokers of SAPALDIA. In the first cases, dTPM10 is defined as the change between SAPALDIA 1 and SAPALDIA 2. In the second cases, dTPM10 is defined as the change in TPM10 between SAPALDIA 1 and the reported time of onset of asthma ('doctors' diagnosed asthma'). Estimates are based on the main model shown in Table 2 and 3 of the main paper (i.e. adjusted for age, gender, baseline atopy, BMI, BHR, and maternal allergies).

Population	Definition of dTPM10 among new cases	N	RR	(95% C.I.)	p-value
All non-smokers	Difference SAPALDIA 1 vrs 2	2390	1.30	(1.05 - 1.61)	0.018
NON-movers only	same	2022	1.52	(1.02 - 2.28)	0.039
All non-smokers	Difference SAPALDIA 1 to time-of-asthma-onset	2390	1.18	(0.93 - 1.49)	0.177
NON-movers only	Same	2022	1.23	(0.80 - 1.89)	0.340