Traffic-related air pollution correlates with adult-onset asthma among never-smokers

N Künzli,[1,2,3,4] P-O Bridevaux,[5] L-J S Liu,[6,7] R Garcia-Esteban,[1,3,4] C Schindler,[6] M W Gerbase,[5] J Sunyer,[1,3,4,8] D Keidel,[6] T Rochat,[5] on behalf of SAPALDIA Team (Swiss Cohort Study on Air Pollution and Lung Diseases in Adults)

ABSTRACT

Background: Traffic-related pollution is associated with the onset of asthma in children. Its effect on adult-onset asthma is poorly investigated. The SAPALDIA cohort study was used to investigate associations between the 11-year change (1991–2002) in home outdoor traffic-related particulate matter up to 10 μm in diameter (TPM_{10}) and the incidence of asthma.

Methods: Never-smokers without asthma at baseline aged 18–60 years in 1991 were eligible for inclusion in the study. Subjects reporting doctor-diagnosed asthma at follow-up were considered incident cases. TPM_{10} at baseline and follow-up was predicted and interpolated to subjects' place of residence by dispersion models using emission and meteorological data. Cox proportional hazard models for time to asthma onset were adjusted (age, gender, baseline atopy, body mass index, bronchial reactivity, maternal allergies).

Results: Of 2725 never-smokers, 41 reported asthma onset in 2002. Home outdoor TPM_{10} concentrations improved during the interval (mean −0.6; range −9 to +7.2; IQR 0.6 μg/m³). The incidence of asthma was associated with a change in TPM_{10}. The hazard ratio (1.30; 95% CI 1.05 to 1.61) per 1 μg/m³ change in TPM_{10} (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 PM_{10} 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.

Currently prevailing levels of ambient air pollutants exacerbate asthma. Thus, asthma-related symptoms, emergency room visits and hospital admissions all increase—together 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 the prevalence of asthma across communities with different levels of pollution did not support this notion.[3] However, cross-community comparisons fail to characterise 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 compared with locations 50–200 m 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 aetiology 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 1000 adults occurring every year.[8] In the younger European Community Respiratory Health Survey (ECRHS), the incidence was 2.3 new cases per 1000 person-years.[9] The first study suggesting an association between home outdoor nitrogen dioxide concentrations (NO_2), used as marker for traffic-related pollution, and adult-onset asthma has only recently been published.[10] The results did not reach statistical significance. Most recently, ECRHS and its Nordic companion study RHINE observed very similar associations between the incidence of asthma and modelled NO_2 concentrations.[11 12] ECHRS was based on a model with a rather limited spatial resolution (1×1 km) 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 an improvement in air quality is associated with an attenuated decline in lung function.[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 so that, among smokers, exposure to these constituents is dominated by smoking, a well accepted cause of asthma.

METHODS

Study design and population

Selection of the study participants and methods of the cross-sectional study (SAPALDIA 1) and the
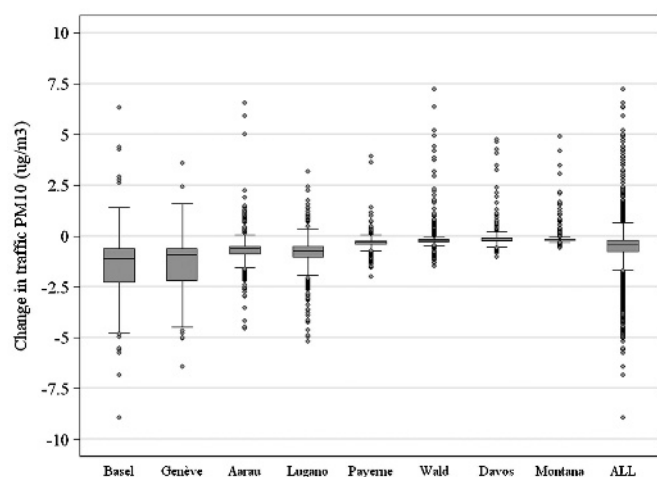
Table 1 Description of study population: lifetime never-smokers with and without incident asthma at SAPALDIA 2

	No asthma (N = 2684)	New-onset asthma (N = 41)	Total (N = 2725)	p Value†
Age at baseline ⩽ 40 years (%)	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 dast/fumes 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 years (%)	66.20	65.85	66.20	0.963
Main street within 20 m (SAPALDIA 1 address) (%)	18.83	17.07	18.81	0.775
Mean (SD) age at follow-up (years)	50.83 (12.25)	45.35 (11.58)	50.74 (12.26)	0.005
Mean (SD) BMI at baseline	23.50 (3.65)	23.67 (3.22)	23.50 (3.64)	0.583
Mean (SD) FEV_1 %predicted at baseline	123.11 (24.93)	116.17 (17.60)	123.00 (24.85)	0.120
Mean (SD) traffic PM_{10} at SAPALDIA 1	2.84 (1.80)	2.42 (1.61)	2.84 (1.80)	0.120
Mean (SD) traffic PM_{10} at SAPALDIA 2	2.25 (1.43)	2.17 (1.43)	2.25 (1.43)	0.126
Mean (SD) total PM_{10} at SAPALDIA 1	27.68 (10.03)	26.46 (10.32)	27.66 (10.04)	0.393
Mean (SD) total PM_{10} at SAPALDIA 2	21.45 (7.17)	21.41 (7.90)	21.45 (7.18)	0.440
Mean (SD) change in total PM_{10}	−6.23 (4.40)	−5.05 (5.02)	−6.21 (4.41)	0.619
Change in traffic PM_{10} (µg/m³) (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	0.59	0.50	0.59	–

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; PM_{10}, particulate matter up to 10 µm in diameter; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung Diseases in Adults.
†p Value for χ^2 test or Kruskal-Wallis test comparing the two groups.

follow-up study (SAPALDIA 2) have been described elsewhere.[16] [17] Random samples of adults (18–60 years) were recruited in 1990 using population registries in eight Swiss areas. Hea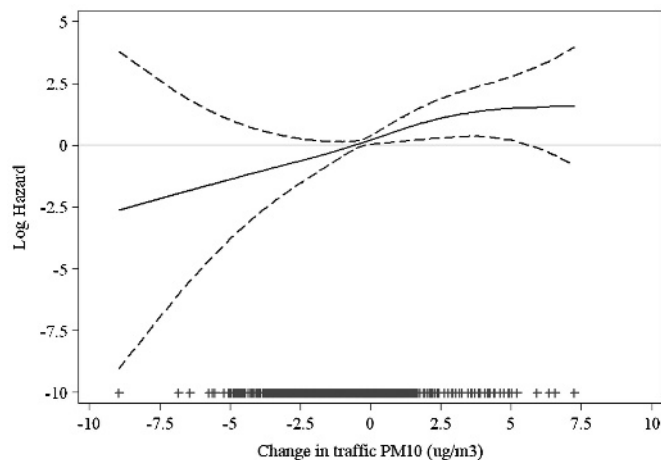lth examinations were conducted in 9651 adults (mean age 40.6 years; 51% women) in 1991 (SAPALDIA 1), with 8047 participants reassessed in 2002 (SAPALDIA 2). There were 5734 participants (71.3%) without asthma or spirometry-defined chronic obstructive pulmonary disease (COPD) at baseline, and with annual home outdoor concentrations of particulate matter up to 10 µm in diameter (PM_{10}) available for both surveys (table 1 and fig 1). The 2725 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

The concentration of PM_{10} was used as a marker of air pollution. Details of the individual assignment of exposure are given in the online supplement. 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 200×200 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] Differences in the annual traffic-related home outdoor PM_{10} concentrations between the two SAPALDIA studies were used 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,

Figure 1 Distribution of the change in traffic-related individually assigned concentrations of particulate matter up to 10 µm in diameter (TPM_{10}) by study area and for the total sample. The eight areas are ordered by the annual mean TPM_{10} at baseline. Negative changes indicate 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 concentrations of particulate matter up to 10 μm in diameter (PM_{10}) and adult-onset asthma (log hazard with 95% confidence interval) among SAPALDIA never-smokers. Generalised additive model adjusted for age, sex, atopy at baseline, body mass index at baseline, bronchial hyperreactivity at baseline, maternal allergies. The symbols (+) on the x-axis indicate observations.

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 TPM_{10}, we discuss the use of changes in regional, secondary and total PM_{10} as part of the sensitivity analyses. Analyses using proximity buffers (20, 50, 75, 100, 150 m) as markers of exposure are discussed in the online supplement.

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?".[16 21] To define onset of doctor-diagnosed asthma, henceforth referred to as "asthma", those with asthma or COPD (forced expiratory volume in 1 s/forced vital capacity (FEV_1/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 hyperreactivity (BHR) based on the standard methacholine inhalation test.[16 22]

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 weal 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 supplement. 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 the incidence of adult-onset asthma and $dTPM_{10}$. Models using the highly correlated TPM_{10} at SAPALDIA 1 and SAPALDIA 2 as well as interval exposures are discussed in the online supplement.

Analyses of incidence were based on Cox proportional hazard regression models. Time to onset of asthma was measured in

years from SAPALDIA 1 to the reported age of first attack, or to SAPALDIA 2 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 $\leqslant 0.2$. 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 (body mass index (BMI), BHR, FEV_1), we also considered the change between SAPALDIA 1 and 2 as potential confounders. Figure 2 was based on a non-parametric regression using Generalised 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 (fig 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 considered 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 2725 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 to 1.88) cases per 1000 person-years. New cases were on average younger and more likely to be atopic at baseline than non-asthmatic subjects. Baseline BHR was also more prevalent among incident cases. Non-participants are described in table S1 in the online supplement.

Traffic emissions were reduced by an average of 25% across all areas between 1990 and 2000.[18] The area mean of the TPM_{10} ranged between 0.9 and 5.4 μg/m³ and between 0.8 and 3.1 μg/m³ in SAPALDIA 1 and 2, respectively, accounting for 6–16% of the total PM_{10} concentrations across the study areas. TPM_{10} was highly variable within areas. The within-area coefficient of variation (CV) ranged from 15% to 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 fig 1. Table S4 in the online supplement 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 μg/m³, with a range from −8.95 to 7.24 and an interquartile range from −0.80 to −0.21 (table 1).

Table 2 shows the asthma incidence hazard ratios for a 1 μg/m³ 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 compared with the unadjusted model or the age- and sex-adjusted basic model (table 2).

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 hyperreactive airways at baseline, reduced the population to 1846 subjects. However, associations with $dTPM_{10}$ remained similar (HR = 1.27; 95% CI 1.01 to 1.61 per μg/m³ $dTPM_{10}$). As shown in table 3, adjustment for change in regional, secondary

Figure 3 Association between incidence of asthma and change in traffic-related concentrations of particulate matter up to 10 μm in diameter (PM_{10}) among subgroups of never-smokers (models adjusted for age, sex, atopy at baseline, body mass index at baseline, bronchial hyperreactivity (BHR) at baseline, maternal allergies). Hazard ratios (HR) are presented per 1 $\mu g/m^3$ difference in traffic-related PM_{10} with 95% confidence intervals (CI); p value for interaction for parental allergies = 0.088; all other interactions p>0.1.
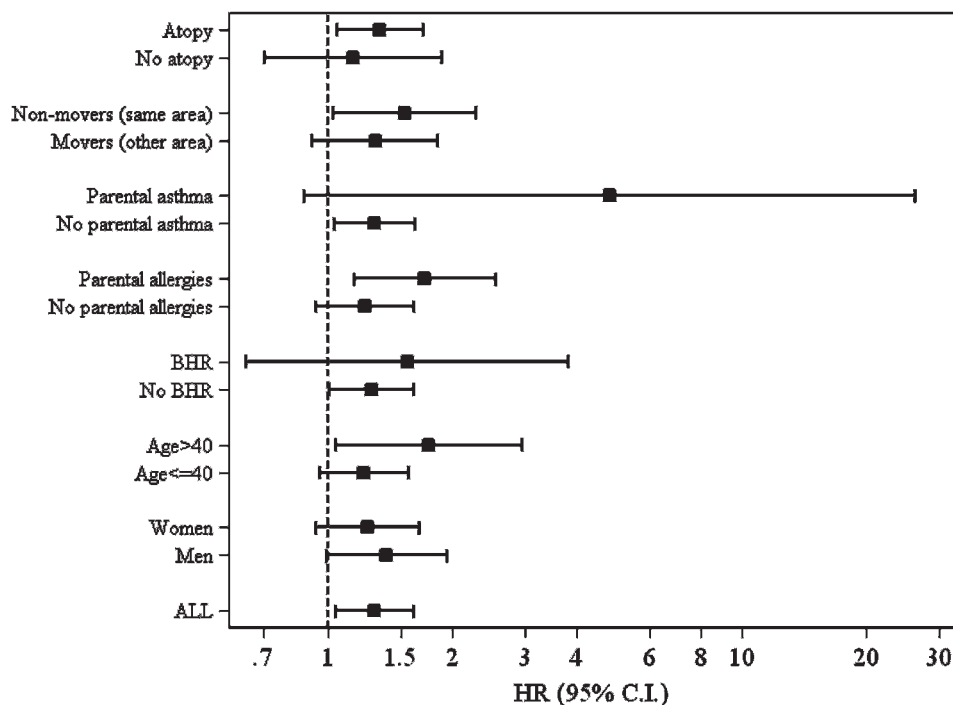
or total PM_{10} did not affect the point estimates for $dTPM_{10}$ but inflated the confidence intervals yielding non-significant estimates. Hazard ratios of the 11-year change in these co-pollutants were instead very sensitive to adjustment by $dTPM_{10}$. The null findings among smokers are shown in table S2 in the online supplement.

Residential proximity to busy roads was not associated with asthma. These results are discussed in the online supplement (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.

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 fig 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 (95% CI 1.02 to 2.28).

DISCUSSION

This study suggests that traffic-related air pollution has a role 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,[2] evidence for a causal role of traffic-related air pollution on childhood asthma onset is strong and more recent studies further support the conclusions of Salam et al.[23] The available individually

Table 2 Association between change in traffic-originated PM_{10} and asthma incidence among SAPALDIA never-smokers

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

BHR, bronchial hyperreactivity; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; HR, hazard ratio; PM_{10}, particulate matter up to 10 μm in diameter; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung Diseases in Adults.
Hazard ratios (HR) are given per 1 $\mu g/m^3$ $dTPM_{10}$ and presented for several models. The first two models include all 41 new cases of asthma; the others are based on 38 new cases due to some missing data in the covariates.
*Includes newly reported asthma at SAPALDIA 2 but age of onset reported as before SAPALDIA 1; age of onset was set to 0.1 years.

Table 3 Association between incidence of asthma and change in traffic-related PM_{10} and other PM_{10} variables among SAPALDIA never-smokers (two-pollutant models)

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

PM_{10}, particulate matter up to 10 μm in diameter.
Hazard ratios (HR) and 95% CI are given per 1 μg/m³ and based on single-pollutant and two-pollutant models, adjusted for age, gender, baseline atopy, body mass index, bronchial hyperreactivity, maternal allergies (main model of table 2). All models include 2390 subjects and 34 new cases of asthma.
Total PM_{10} is the sum of all PM_{10} and thus includes traffic-related PM_{10}.

assigned long-term characterisation 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 of developing asthma as an adult, or an increase in pollution correlates with a larger number of cases of adult-onset asthma.

The results need to be put in the 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* for successfully investigating the asthma-onset hypothesis. Our primary exposure term was the change in TPM_{10}. 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 a subject's exposure history. The only adequate alternative approach to our analysis would be the use of the interval exposure with adjustment for baseline TPM_{10}, which corresponds conceptually and mathematically to our use of the *change* in TPM_{10}. 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 5–10 times in concentration along the traffic arteries while decreasing to "urban background" concentrations within 200 m of such roads.[4 24] 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 200×200 m.[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 commuting. This misclassification may attenuate estimates, but we expect little bias as home outdoor remains the most important determinant of personal exposure to pollutants of outdoor origin.[25]

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 $PM_{2.5}$, ultrafine particles, polycyclic aromatic hydrocarbons 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 "TPM_{10}" captures in part also 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 is discussed in the online supplement.

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 $dTPM_{10}$ (eg, PM_{10} 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 the development of asthma.

As emphasised 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-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, so 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 (see online table 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 TPM_{10} was derived as the

difference between SAPALDIA 1 and 2. The theoretically more appealing definition of the exposure window until asthma onset is discussed in the online supplement. These attenuated and non-significant findings must be interpreted with caution.

The identification of susceptible subgroups is of both public health and biological relevance. Given the limited number of new cases, we can only speculate about the meaning of the patterns shown in fig 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 atopic subjects.[10]

The onset of asthma among smokers—another group with an inherently higher incidence of asthma—was not associated with TPM_{10} (see table S2 in the online supplement). If similar combustion-related constituents and immunological mechanisms were involved in asthma onset due to both smoking and traffic-related pollution, the contribution of the latter exposure may be marginal among smokers, resulting in null findings for TPM_{10}.

The study by Modig *et al* was the first to use a marker of local traffic-related pollution (namely NO_2) to investigate the asthma-onset hypothesis in adults. While their findings are in line with our results, the correlations were not statistically significant in the Swedish case-control study ($N = 2\times203$).[10] It is also of note that traffic-related PM_{10} at SAPALDIA 2 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. One may therefore 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 the incidence of asthma also correlated significantly with home outdoor NO_2 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] so the positive results contrast with the null findings seen in our study if exposure at SAPALDIA 2 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 to ECRHS, but was based on an NO_2 dispersion model of high resolution (50×50 m).[12] Our use of TPM_{10} 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 years) and only three urban areas.

While the Seventh Day Adventist study (AHSMOG) reported an association between the incidence of asthma 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 characterised.[16 21] Time, location and population characteristics differ substantially 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 to be 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.[26–28] This results in oxidative stress and both local as well as systemic inflammation, which are considered key pathways in the development of asthma.[26 29] Experimental studies confirm an adverse role in IgE-mediated allergic responses which may play a role in asthma development among atopic subjects.[30] Our data suggest the latter to be more strongly affected by traffic-related pollution. Respective findings in 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 a much larger sample size of asthma cases would greatly attenuate all the limitations faced in this study.

REFERENCES

1. **Eder W,** Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;**355**:2226–35.
2. **Salam MT,** Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. *Curr Opin Pulm Med* 2008;**14**:3–8.
3. **Brunekreef B,** Holgate ST. Air pollution and health. *Lancet* 2002;**360**:1233–42.
4. **Zhou Y,** Levy JI. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. *BMC Public Health* 2007;**7**:89.
5. **Metsala J,** Kilkkinen A, Kaila M, *et al*. Perinatal factors and the risk of asthma in childhood—a population-based register study in Finland. *Am J Epidemiol* 2008;**168**:170–8.
6. **Jaakkola MS,** Jaakkola JJ. Office work exposures and adult-onset asthma. *Environ Health Perspect* 2007;**115**:1007–11.
7. **Le Moual N,** Kauffmann F, Eisen EA, *et al*. The healthy worker effect in asthma: work may cause asthma, but asthma may also influence work. *Am J Respir Crit Care Med* 2008;**177**:4–10.
8. **Barr RG,** Wentowski CC, Curhan GC, *et al*. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;**169**:836–41.
9. **Zock JP,** Plana E, Jarvis D, *et al*. The use of household cleaning sprays and adult asthma: an international longitudinal study. *Am J Respir Crit Care Med* 2007;**176**:735–41.
10. **Modig L,** Jarvholm B, Ronnmark E, *et al*. Vehicle exhaust exposure in an incident case-control study of adult asthma. *Eur Respir J* 2006;**28**:75–81.
11. **Jacquemin B,** Sunyer J, Forsberg B, *et al*. Home outdoor NO_2 and new onset of self-reported asthma in adults. *Epidemiology* 2009;**20**:119–26.
12. **Modig L,** Toren K, Janson C, *et al*. Vehicle exhaust outside the home and onset of asthma among adults. *Eur Respir J* 2009 Feb 27 [Epub ahead of print].
13. **Hazenkamp-von Arx ME,** Gotschi T, Ackermann-Liebrich U, *et al*. PM2.5 and NO2 assessment in 21 European study centres of ECRHS II: annual means and seasonal differences*1. *Atmos Environ* 2004;**38**:1943–53.
14. **Beelen R,** Hoek G, Pebesma E, *et al*. Mapping of background air pollution at a fine spatial scale across the European Union. *Sci Total Environ* 2009;**407**:1852–67.
15. **Downs SH,** Schindler C, Liu LJ, *et al*. Reduced exposure to PM10 and attenuated age-related decline in lung function. *N Engl J Med* 2007;**357**:2338–47.
16. **Martin BW,** Ackermann-Liebrich U, Leuenberger P, *et al*. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. *Soz Praventivmed* 1997;**42**:67–84.
17. **Ackermann-Liebrich U,** Kuna-Dibbert B, Probst-Hensch NM, *et al*. Follow-up of the Swiss Cohort study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991–2003: methods and characterisation of participants. *Soz Praventivmed* 2005;**50**:245–63.
18. **Liu L-JS,** Curjuric I, Keidel D, *et al*. Characterisation of source-specific air pollution exposure for a large population-based Swiss cohort (SAPALDIA). *Environ Health Perspect* 2007;**115**:1638–45.
19. **Bundesamt für Umwelt, Wald und Landschaft (BUWAL)**. Modelling of PM10 and PM2.5 ambient concentrations in Switzerland 2000 and 2010. *Schriftenreihe Umwelt* 2003;Nr 169.
20. **Bundesamt für Umwelt, Wald und Landschaft (BUWAL)**. Modellierung der PM10-Belastung in der Schweiz. *Schriftenreihe Umwelt* 1999;Nr 310.
21. **Burney PG,** Luczynska C, Chinn S, *et al*. The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–60.
22. **Chinn S,** Burney P, Jarvis D, *et al*. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1997;**10**:2495–501.
23. **Jerrett M,** Shankardass K, Berhane K, *et al*. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008;**116**:1433–8.
24. **Morawska LR,** Ristovski Z, Jayaratne Z, *et al*. Ambient nano and ultrafine particles from motor vehicle emissions: characteristics, ambient processing and implications on human exposure. *Atmos Environ* 2008;**42**:8113–38.
25. **Rojas-Bracho L,** Suh HH, Koutrakis P. Relationships among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. *J Expo Anal Environ Epidemiol* 2000;**10**:294–306.
26. **Nel A.** Air pollution-related illness: effects of particles. *Science* 2005;**308**:804–6.
27. **Nel AE,** Diaz-Sanchez D, Li N. The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. *Curr Opin Pulm Med* 2001;**7**:20–6.
28. **Künzli N,** Mudway IS, Gotschi T, *et al*. Comparison of oxidative properties, light absorbance, total and elemental mass concentration of ambient PM2.5 collected at 20 European sites. *Environ Health Perspect* 2006;**114**:684–90.
29. **Gilliland FD,** McConnell R, Peters J, *et al*. A theoretical basis for investigating ambient air pollution and children's respiratory health. *Environ Health Perspect* 1999;**107**(Suppl 3):403–7.
30. **Gilliland FD,** Li YF, Saxon A, *et al*. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet* 2004;**363**:119.

ONLINE SUPPLEMENT TO:

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)

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		Participants		
	N = 68		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 allergies 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