ONLINE SUPPLEMENT TO:

TITLE:

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

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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