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Title page

Traffic related particle matter exposure, lung function effects and potential interactions in a cohort study

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ABSTRACT

objectives: To investigate the long-term effects of source-specific particle matter (PM) on lung function, effects of genetic variants of Surfactant Protein A (SP-A) and glutathione S-transferase (GST) genes GSTP1 and GSTT1, and effect modification by single nucleotide polymorphism (SNP) genotype.

design: Cohort study with address-based annual PM exposure assigned from annual estimates of size (PM_{10}, $PM_{2.5}$ and PM_{BC}) and source-specific (traffic, industry, marine traffic and wood burning) dispersion modelling.

setting: Gothenburg, Sweden.

participants: The ADONIX study had 6685 participants recruited from the general population, of which 5216 (78%) were eligible for inclusion in the current study with European ancestry and information on all variables of interest. Mean age was 51.4 years (range 24-76) and 2427 (46.5%) were males.

primary and secondary outcome measures: The primary outcome was forced vital capacity (FVC) and forced expiratory flow in 1 second (FEV_1). The secondary outcome measure was effects and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

results: Exposure to traffic-related PM_{10} and $PM_{2.5}$ was associated with decreases in percent-predicted FEV_1 by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per interquartile range (IQR), respectively, and with decreases in percent-predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and –0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM_{BC} was strongly associated with both FEV_1 and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%), respectively, for FVC, and similarly for FEV_1. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs showed effect modification with exposure to $PM_{2.5}$ from industry and marine traffic.

conclusions: PM exposure, specifically traffic-related, was associated with FVC and FEV_1 reductions and not modified by genotype. Genetic effect modification was suggested for industry and marine traffic $PM_{2.5}$.

Article summary: Strength and limitations of this study

- An extensive dispersion model of source-specific PM was assigned to a large, general population cohort of adults in a single urban region
- The cohort was designed with focus on respiratory health and many covariates were collected as well as genotyping for genes with known associations with respiratory health
- Data collection was performed according to a standardized maneuver by trained personnel although spirometry was not performed with reversibility test
- Residential history was not available, so exposure is only assigned for the time of inclusion into the study, which also does not take indoor or occupational air pollution into account.

INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function[1 2] and accelerated lung function decline.[3] However, evidence on specific importance of different particle sizes and sources is still limited,[4] and are to date addressed in only few epidemiological studies of respiratory health effects with non-conclusive results.[2 5 6] In panel studies, high levels of traffic PM had stronger association than total PM with short term increases in Club Cell protein CC16 (a marker of increased lung permeability) concentration in urine[7], and in controlled experiments, *in vitro* exposure of human BEAS-2B lung cells to PM from different sources triggered very different pulmonary cell and DNA damage outcomes.[8] A deepened knowledge about effects of specific particle pollution sources is thus of particular interest to prioritize public health measures to reduce health effects of ambient air pollution, and this field of research is expanding rapidly.[9]

It is only in rare cases that pollution sources be definitely identified by specific chemicals, as individual chemicals may be present in more than one source. Rather, profiles are built from particle size distributions and the relative concentrations of specific chemicals. Traffic pollution is for example characterized by NOx and ultrafine particles, whereas particles from petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and lanthanum.[10] Particles from other industry is characterized by high levels of trace metals vanadium and nickel,[10 11] but are of course sector-dependent. Similarly, PM from marine traffic is subject to large uncertainties as fuel types and fleet types vary across the world, rendering study results ungeneralizable.[12]

Beyond the importance of exposure composition and source, individual susceptibility to air pollution is modified by many factors, including genotype. Susceptibility related to genetic variability may improve our understanding of the physiological mechanisms underlying health effects of air pollution.[13 14] Glutathione S-transferase (GST) enzymes are involved in metabolizing reactive oxygen species to reduce oxidative stress.[15] GSTP1 SNPs have been reported to modify the risk of cardiovascular disease associated with exposure to NO_2[16] and modify the association between NO_2 and

lung function decline in adults,[17] but findings are inconsistent and no meta-analysis has been performed.[18 19] Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has important functions in the innate immune system of the lungs, especially for opsonizing inhaled material.[20] SNPs in SP-A coding regions have been associated with multiple respiratory diseases,[13 21] and suggested gene-environment interactions for smoking and chronic obstructive pulmonary disease.[22]

Many questions remain as to what components of air pollution are harmful in a general population, in particular at relatively low pollution exposures, and if such associations are modified by genetic factors. Thus, the aim of the current study was to investigate the effects of different PM sources on lung function in a general population cohort using epidemiological methods and to investigate lung function effects of genotype and gene-environment interaction with source-specific particle exposures.

METHODS

Study population

The study population originates from the ADONIX (ADult-Onset asthma and NItric oXide) cohort, a random sample of subjects aged 24-76 years who were invited to participate in a clinical examination between 2001-2008 as previously described.[16 23-26] In brief, the overall participation rate was 46%, all participants provided data on residential address, lifestyle factors and education, presence of allergic airway inflammation and respiratory health, as well as clinical measurements of lung function, such as spirometry (single manoeuver) and nitric oxide in exhaled air (FENO). Blood samples were collected for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1 genes.

Exposure assessment

As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter

(PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using dispersion modelling described in detail in Segersson and colleagues.[27] PM_{10} and $PM_{2.5}$ represent particles smaller than 10 and 2.5 micrometers (µm) respectively, whereas black carbon particles, PM_{BC}, are soot particles from combustion, notably vehicle exhaust. The specific sources were traffic (exhaust and road wear for PM_{10} and $PM_{2.5}$, exhaust only for PM_{BC}), residential heating (predominantly house heating using wood assessed as area sources), marine traffic (averaged description from a bottom-up calculation using actual positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in Gothenburg dominated by refineries, energy plants, and other industry).[28] Background concentration (long-range transport particles), was also provided, but was estimated indirectly as the difference between total modelled local contribution and monitoring data from a central urban background station. Consequently, it showed no spatial variation and was not used for analyses. To refine the estimated contribution of traffic, an increment due to reduced ventilation in the street canyons was added for the busiest streets. The increment was estimated as the difference between simulations with and without buildings using the OSPM model.[29] For each study participant's residential address at the date of clinical examination, annual mean values of pollutants were calculated separately for five source categories and modelled exposure grid values of all PM fractions were matched to the year of the participant's clinical examination.

Outcome definitions

Dynamic spirometry including FEV_1 and FVC was performed with the subject in a sitting position using a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.[30] A local reference material was used for calculation of percent predicted (% predicted) of FEV_1 and FVC and lower limit of normal, (LLN, the lower 5^{th} percentile in healthy individuals) for FEV_1 and FVC.[31 32] Asthma was defined as reporting having had at least one asthma attack in the previous 12 months,

and atopy was defined as having a positive phadiatop test. We used FEV_1, FVC and FEV_1/FVC below LLN as an indicator of clinically significant lung function reductions or air flow limitation.

Based on questionnaire replies, smoking status was categorised into current, former (no smoking during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles within residential regions, postcodes were categorised into four regions: Inner city, non-central city, suburban, and outer suburb or rural. Education was categorised in six categories: elementary school, lower secondary school, training or girls' school, grammar school, university, and "other" or not reported. Individuals who did not have information on the variables of interest were excluded, except for genotype, where analyses were run separately for each SNP. For this study we used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common) allele. Individuals with self-reported non-European background were excluded from the analysis (n=315).

Statistical methods

First, descriptive statistics were calculated for the cohort and exposure data, and correlations between the total and source-specific exposure estimates for all PM size fractions were determined.

We estimated the association between each PM size fraction for each PM source, with FEV_1 and FVC, in linear models. First, lung function effects associated with PM size fractions and sources were analysed with exposure as a continuous variable, and estimated for an interquartile increase in exposure. Second, we investigated the effects of the highest exposure values by setting high exposure cutoff for PM above the 90^{th} percentile of population exposure, medium exposure at 50-90^{th} percentile, with exposure at or below 50^{th} percentile as the reference, and tested these for linear trends. To investigate clinically significant effects, we modelled increased risk of low lung function in logistic models with LLN as a cut-off. To assess confounding, covariates were added to regression models and were retained if the estimate of the main effect was altered by more than 10% by their inclusion. The covariates included in the final models were age, sex, weight, education, residential

postcode region, smoking status, and exposure to passive smoking in the last 12 months. For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes and lung function for all available SNPs in single-SNP linear models. To evaluate effect modification, we tested for interaction of the effects of exposure to different PM size fractions and sources on lung function by genotype, using a likelihood ratio tests comparing the model with interaction term to the model without this term. Similarly, the analyses of PM effects were also stratified by sex and respiratory health status as well as smoking status, asthma status, atopic status, BMI, age categories to evaluate possible confounding from any of these characteristics.

All regression results for change in lung function were reported as increment or decrement in % predicted. Odds ratios were obtained from the logistic model analyses. All results are presented as point estimates with 95% confidence intervals, and with p-values as appropriate. Analyses were performed in R studio[33] using the package "phia" (post-hoc interaction analysis).[34]

RESULTS

The ADONIX cohort includes 6685 individuals, of which 5216 were included with information on the variables related to exposure and health outcomes used in this study and self-reported European ancestry. The mean age of the study population was 51.6 ±11.4 years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and 10.2% were exposed to passive smoking. A total of 9.5% of individuals had FEV_1 below lower limit of normal and 9.5% had FVC below LLN. The most common highest education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
Females	2789 (53.5%)
Respiratory health	

FEV_1 (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV_1, n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV_1/FVC, n (%)	548 (10.5%)
Smoking	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)
Passive smoking (last 12 months)	534 (10.2%)
Education	
Elementary school, n (%)	639 (12.2%)
Lower secondary School, n (%)	175 (3.3%)
Training/girls school, n (%)	389 (7.5%)
Grammar school, n (%)	1205 (23.1%)
University, n (%)	1954 (37.5%)
Other or not reported, n (%)	853 (16.4%)
Residential area	
Inner city, n (%)	945 (18.1%)
Non-central urban, n (%)	922 (17.7)
Suburban, n (%)	2178 (41.7%)
Outer suburb or rural, n (%)	1171 (22.4%)

*Lung function predicted from age, height and sex (Brisman et al., 2017) FEV_1, forced expiratory volume in 1 second.

FVC, forced vital capacity.

LLN, lower limit of normal, the fifth percentile of a healthy population, according to formula from Brisman et al., 2017.

The mean annual air pollution levels at the residential addresses in the study population at study entry were moderate, at 15.7 µg/m^3 PM_{10}, 9.3 µg/m^3 $PM_{2.5}$, and 0.76 µg/m^3 PM_{BC} (Table 2). Background long-range transport constituted the main source of exposure, contributing to 75% and 76% of PM_{10} and

$PM_{2.5}$ levels respectively. The local emission source that contributed most to total PM_{10} was traffic, whereas residential heating contributed most to $PM_{2.5}$ (Table 2).

TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION

PM species and sources	Mean (standard deviation)	50th percentile	90th percentile	IQR
PM_{10} total	15.7 (2.49)	15.47	18.80	3.05
Traffic (μg/m³)	2.32 (1.75)	1.78	4.41	1.64
Residential heating (μg/m³)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m³)	0.03 (0.05)	0.02	0.08	0.03
Industry (μg/m³)	0.11 (0.09)	0.09	0.23	0.10
$PM_{2.5}$ total (μg/m³)	9.33 (1.75)	9.36	11.80	2.47
Traffic (μg/m³)	0.74 (0.56)	0.57	1.41	0.52
Residential heating (μg/m³)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m³)	0.03 (0.05)	0.05	0.08	0.03
Industry (μg/m³)	0.07 (0.05)	0.06	0.12	0.06
PM_{BC} total (μg/m³)	0.76 (0.32)	0.71	1.13	0.33
Traffic (μg/m³)	0.36 (0.29)	0.27	0.69	0.25
Residential heating(μg/m³)	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (μg/m³)	0.01 (0.01)	0.00	0.02	0.01
Industry (μg/m³)	0.01 (0.01)	0.01	0.01	0.01

IQR, interquartile range.

Traffic was the largest contributor to PM_{BC}, and for PM_{BC} the contribution from long-range sources was considerably lower than for PM_{10} and $PM_{2.5}$, 26%. Traffic sources were originally divided into exhaust and road wear, but as these were highly correlated (r>0.98), we refrained from separating the two in the analyses, using instead a single variable for traffic exposure. The correlation between total and traffic-related exposure was very high for PM_{BC} (r=.99), whereas it was high for PM_{10} (r=.75) and moderate for $PM_{2.5}$ (r=.40) (Table S3).

Effects of PM exposure

Most PM sources were negatively associated with percent predicted lung function, and estimates for PM_{BC} overall and from traffic, and for $PM_{2.5}$ and PM_{10} from traffic, reached statistical significance for reductions in FEV_1 and FVC. The effect estimates for particles from residential heating, marine traffic or industry indicated no strong or consistent adverse effects in the linear models (Table 3).

TABLE 3 CHANGE IN FEV_1 AND FVC PER IQR CHANGE IN PM FROM DIFFERENT SOURCES

	Delta % predicted FEV_1				Delta % predicted FVC			
	B	95% CI			*B*	95% CI		
		Lower	Upper	p-value		Lower	Upper	p-value
PM_{10} Total	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	**-0.48**	**-0.89**	**-0.07**	**0.02**	**-0.46**	**-0.83**	**-0.08**	**0.02**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.24	0.24	1.00	-0.05	-0.27	0.17	0.66
Industry	-0.33	-0.78	0.11	0.14	-0.40	-0.80	0.01	0.05
$PM_{2.5}$ Total	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	**-0.47**	**-0.88**	**-0.07**	**0.02**	**-0.47**	**-0.83**	**-0.10**	**0.01**
Residential	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91

heating								
Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
PM_{BC} Total	**-0.56**	**-1.01**	**-0.12**	**0.01**	**-0.53**	**-0.94**	**-0.13**	**0.01**
Traffic	-0.41	-0.78	-0.03	0.03	**-0.43**	**-0.77**	**-0.09**	**0.01**
Residential heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
Industry	-0.40	-0.92	0.12	0.13	-0.38	-0.85	0.09	0.11

Parameter coefficients from in separate, single-pollutant models adjusted for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

IQR, interquartile range.

In models with exposure categorized (low, medium, and high exposure), there was a consistent trend across categories for traffic-related exposure to all particulate measures for both FVC and FEV_1 (*p* for trend<0.05; for FEV_1 and PM_{BC} traffic p=0.09; the trend was slightly less strong and consistent for total exposure. There were no significant negative associations between exposure to particles of any size from residential heating, marine traffic or industrial sources and lung function (Figure 1), nor were there consistent trends (Table S4). For the odds of having FEV_1 and FVC below LLN, we observed a very similar pattern, with high exposure to all particle measures from traffic showing an increased risk of having reduced FEV_1 and FVC (p<0.05; except p=0.08 for FEV_1 and PM_{BC}) (Table S5). FEV_1/FVC below LLN was not associated with any exposure (data not shown).

Genetic main effects

The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%. (Table S1). In a main effect genetic analysis without considering environmental exposure, minor allele carrier status of three GST SNPs was associated with lung function outcomes. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV_1 reductions by -0.80% (p=0.044) and -0.90%

(p=0.017), respectively, and FVC reductions were seen in minor allele carriers of the same GSTP1 SNP rs762803 (-0.74%, p=0.042) and the GSTT1 null genotype assessed with SNP rs2266637 (-1.434%, p=0.001). No main effect associations were found with SP-A SNPs (Table S1).

Effect modification of PM effects

$PM_{2.5}$, which had marginally more consistent effects for traffic-related exposure, was used for interaction analyses. The effect of genotype and exposure to $PM_{2.5}$ from all sources was analysed in interaction models, and SNPs with exposure-interaction p-values lower than 0.1 are shown in Table S2. The number of significant interactions was higher than expected by chance. The most plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV_1 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result should, however, be seen as highly exploratory. Stratifying data by smoking status, atopy, asthma status, and BMI category showed no effect modification on the estimates for air pollution effects in both linear and logistic analysis (data not shown).

DISCUSSION

In a general population cohort exposed to moderate levels of PM air pollution in a global perspective, modelled exposure to PM_{10} and $PM_{2.5}$ from traffic, as well as PM_{BC} were associated with reductions in FVC and FEV_1 in linear models, a pattern also consistently shown for high exposure in analyses with categorized exposure, and for risk of reduced FEV_1 or FVC (below LLN) in logistic regression. We observed no associations for airflow limitation (FEV_1/FVC below LLN). In this study, efforts were made to create source-specific exposure estimates, but it should be recognized that these are associated with different levels of uncertainty. Observing consistent associations between traffic-related exposure, and similar effect estimates for total exposure, but not for other sources of PM we speculate involvement of source-specific effects. However, these observations could be due to the more accurate spatial estimation of traffic, whereas the exposure estimates for both marine traffic, industry and residential heating may be less accurate.[27]

In the current study, we found the most consistent associations between both FEV_1 and FVC and traffic related particles, which is not surprising as the traffic-related pollutants with the street canyon have a higher degree of accuracy than the other pollutant sources. No obvious associations were seen between any fraction of PM from residential heating, marine traffic or industry on lung function, but their relative contribution to total PM was modest.

Although there were no associations between $PM_{2.5}$ from residential heating, marine traffic or industry on FEV_1 and FVC, we saw some exploratory but potentially interesting interaction patterns for some genotypes with industrial PM exposure, indicating that effects from industrial exposure may be less general than that of traffic particles, being concentrated within individuals with genetic susceptibilities.[13] Industrial exposure in Gothenburg is concentrated along the Götaälv river and is dominated by a power plant and oil refineries.

In spite moderate to high correlations between the three traffic related PM fractions (Table S3), total PM_{10} and $PM_{2.5}$ were not significantly associated with FVC and FEV_1, although the direction of effect

was consistent with that from traffic PM_{10} and $PM_{2.5}$. Residential heating is the second largest local contribution to total PM, and we observed negative correlations between PM from residential heating and total PM as well as PM from other sources. PM from residential heating might thus be interpreted as an indicator of low exposure to other sources of air pollution which might contribute to explaining the few suggested inverse (positive) associations seen in some categorical analyses between PM from residential heating and FEV_1 and FVC (e.g. Figure 1).

In a previous study of the same cohort material, short distance to the nearest road was found to be associated with decreases in FEV_1 and FVC.[35] The pollution levels found in the current study were moderate compared to those presented in the study from Adam and colleagues.[6] In a meta-analysis of the ESCAPE data, that study found significant associations for both FEV_1 and FVC in adults related to long-term exposure to NO_2, NOx and PM_{10}, but not $PM_{2.5}$ or coarse PM. In our data, modelled annual averages of NOx and NO_2 were available for parts of the cohort for some years, and both were highly correlated with traffic PM_{10}, $PM_{2.5}$ and PM_{BC} (all correlations r>0.79).

Effects specifically of exposure to industrial emissions has not been widely studied, and industry emissions are often pooled with other sources,[27] or considered negligible as high stacks disperse the emissions.[36] Studies of respiratory health with source specific results generally find associations mainly with traffic: In the study of Jacquemin and colleagues,[7] only traffic, and not industry-specific particles were associated with the lung damage marker CC16. Krall and colleagues[9] observed only effects from tailpipe exhaust on lung function and eNO. Billet and colleagues[8] exposed cells *in-vitro* to particles from a highly industrialized environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response. Peng and colleagues[5] observed that PM from vehicle emissions, diesel engines and wood burning were associated with the largest increases in emergency hospital admissions for CVD and respiratory disease.[5] In a multi-city European study[37] there were negative associations between FEV_1 and PM from

nickel and sulphur, however results were not consistent between cities, perhaps reflecting the heterogeneity in particle compositions in different cities in the study.[38]

For the two SP-A1 SNPs that had potential interactions of interest with industry PM in our study, other studies have found rs1059057 to be associated with lung injury[39] and cystic fibrosis,[40] and rs1136451 with susceptibility to COPD,[22] but only gene-environment effects from tobacco smoking were addressed in these studies. GSTP1 SNP rs1695 was previously associated with possible increased asthma risk of air pollution exposure,[18] and we found a main effect associated with lower FEV_1 in the current study of adults. These genetic results should be seen as exploratory and be interpreted with caution.

The cohort data used in this study were collected to study respiratory health, and provides a rich dataset containing a large number of variables of interest. In the model selection, adding additional covariates as potential confounders did not affect the regression estimates substantially. Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered 2001–2003) and showed that women, the elderly, and individuals with university educated were more likely to participate.[26] As we adjusted for these covariates and as exposure was unknown to participants, this is not very likely to bias the current results.

The number of individuals who fell below the lower limit of normal for both FEV_1 and FVC was rather high, as this value is defined as the 5^{th} percentile in a healthy, non-smoking population. It is possible that individuals with respiratory issues are more likely to take part in a study such as ADONIX. On the other hand, with clinical outcome measures and an exposure which was not known to the participants, this is an unlikely source of important bias.

In this study, complete residential histories, including duration of residence, were not available. Instead, we used a single modelled value for residential exposure that was matched by year of participation for each individual, rather than a complete longitudinal exposure history over multiple

years. We consider this a reasonable approach, as the between-year correlation in air pollution concentrations and emissions in a certain location is very high.

As people spend a sizable proportion of their time outside the home, our results are based on modelled air pollution data, and thus represents an approximation of the real exposure although this is an established method. The resulting misclassification of exposure would, however, then to reduce risk estimates. The model was developed using new emissions inventories, updated information on vehicle composition, and had been further verified by measurements.[27] However, for residential heating, the source assignment is based on proxies such as building type, as no actual source inventory was available.

The very high correlations between traffic-related PM_{10}, $PM_{2.5}$ and PM_{BC} (Table S3) mean that it is difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to high correlations between the various PM source measures also meant we had to refrain from using multi-pollutant models, meaning that interpretation of estimates associated with each exposure type must be interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent associations with FEV_1 and FVC, whereas the other source-specific exposures did not.

CONCLUSION

In this large study of clinically measured outcomes in a general population sample we found that exposure to traffic particles of all three studied size fractions was associated with reductions in FEV_1 and FVC and increased risk of low FEV_1 and FVC (below LLN), supporting the need for measures to reduce urban pollution from traffic to protect urban populations. Furthermore, we found intriguing suggestions that the SP-A1 gene may play a part in susceptibility to air pollution from industrial sources, possibly due to its very different composition.

Author contribution

HKC analysed the data and drafted the manuscript. FN and A-CO provided the cohort and genetic data, contributed to essential parts of the introduction and discussion and the final manuscript. DS provided and documented the PM exposure data. All authors approved the final version of the manuscript.

Data statement

Additional data from the ADONIX study exist and are held by the authors.

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Competing interests

None declared.

Legends

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50_{th} to 90_{th}) and high (above 90_{th} percentile) concentration of source-specific PM

Figure 2 a-e Gene-environment interactions of selected SNPs and FEV1 and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

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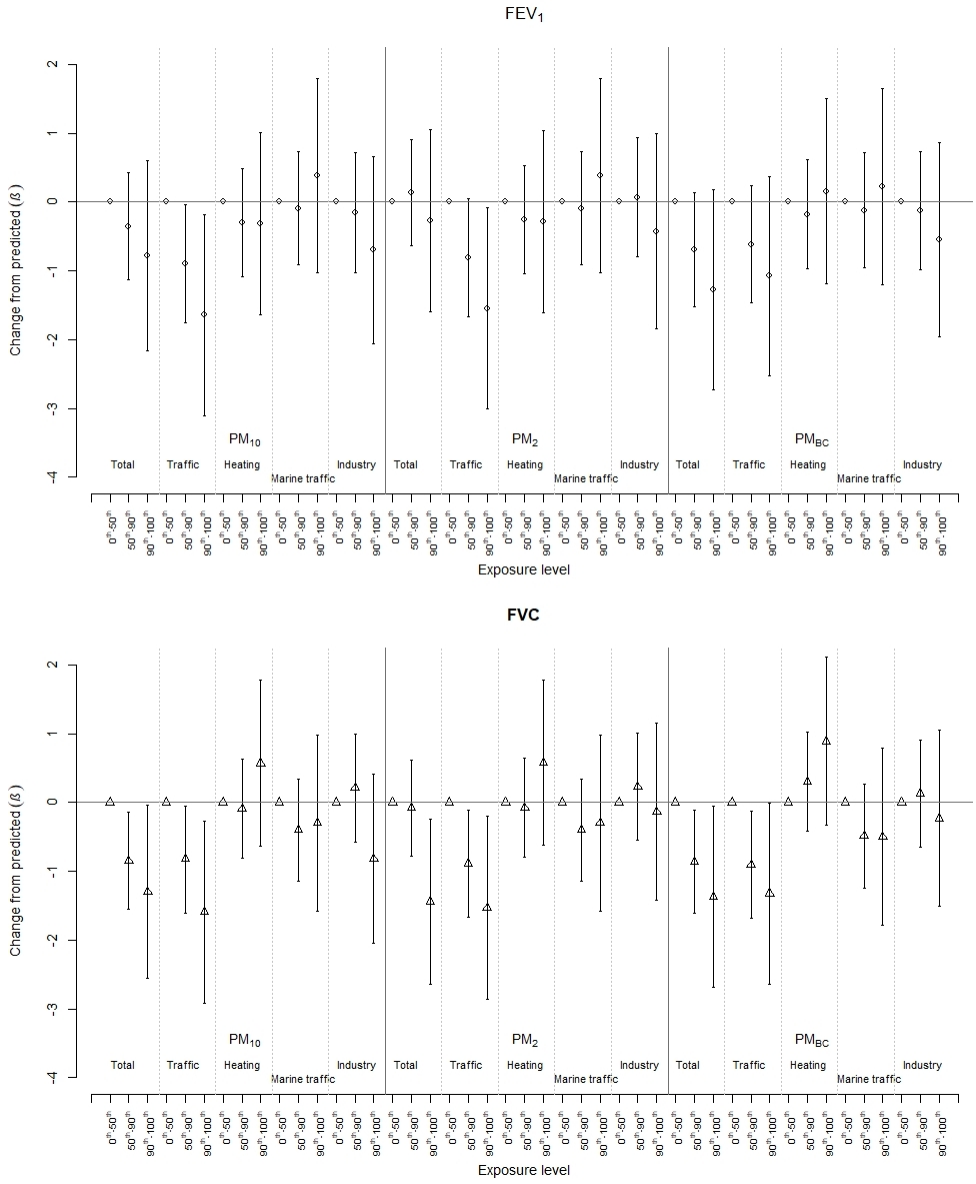
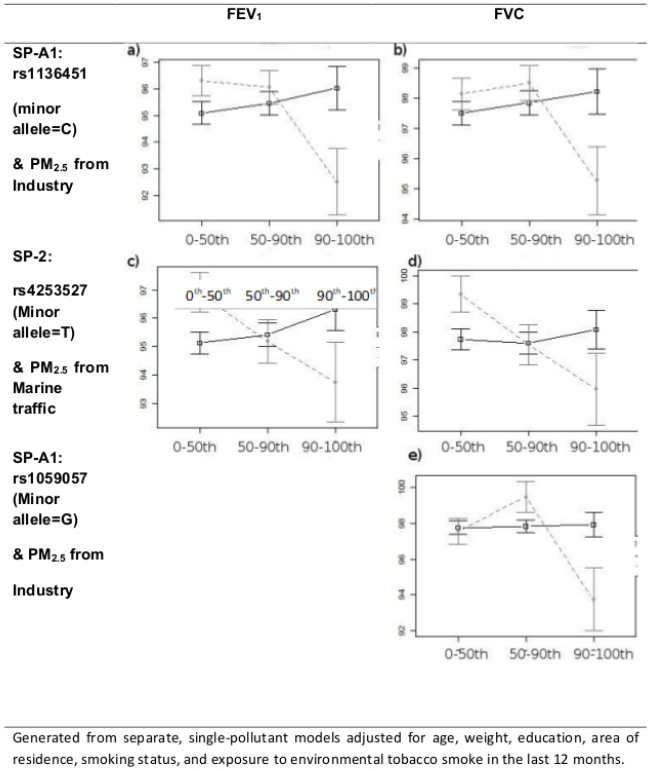


Figure 1 Change in $FEV_{1<sub/>}$ and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

352x423mm (72 x 72 DPI)



Generated from separate, single-pollutant models adjusted for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

Figure 2 a-e Gene-environment interactions of selected SNPs and FEV1 and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

209x296mm (100 x 100 DPI)

Title page

Traffic related particle matter exposure, lung function effects and potential interactions in a cohort study

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PM size fractions, PM sources, lung function, GST, SP-A, gene-environment interaction

ABSTRACT

objectives: To investigate the long-term effects of source-specific particle matter (PM) on lung function, effects of genetic variants of Surfactant Protein A (SP-A) and glutathione S-transferase (GST) genes GSTP1 and GSTT1, and effect modification by single nucleotide polymorphism (SNP) genotype.

design: Cohort study with address-based annual PM exposure assigned from annual estimates of size (PM_{10}, $PM_{2.5}$ and PM_{BC}) and source-specific (traffic, industry, marine traffic and wood burning) dispersion modelling.

setting: Gothenburg, Sweden.

participants: The ADONIX study had 6685 participants recruited from the general population, of which 5216 (78%) were eligible for inclusion in the current study with European ancestry and information on all variables of interest. Mean age was 51.4 years (range 24-76) and 2427 (46.5%) were males.

primary and secondary outcome measures: The primary outcome was forced vital capacity (FVC) and forced expiratory flow in 1 second (FEV_1). The secondary outcome measure was effects and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

results: Exposure to traffic-related PM_{10} and $PM_{2.5}$ was associated with decreases in percent-predicted FEV_1 by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per interquartile range (IQR), respectively, and with decreases in percent-predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and –0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM_{BC} was strongly associated with both FEV_1 and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%), respectively, for FVC, and similarly for FEV_1. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs showed effect modification with exposure to $PM_{2.5}$ from industry and marine traffic.

conclusions: PM exposure, specifically traffic-related, was associated with FVC and FEV_1 reductions and not modified by genotype. Genetic effect modification was suggested for industry and marine traffic $PM_{2.5}$.

Article summary: Strength and limitations of this study

- An extensive dispersion model of source-specific PM was assigned to a large, general population cohort of adults in a single urban region
- The cohort was designed with focus on respiratory health and many covariates were collected as well as genotyping for genes with known associations with respiratory health
- Data collection was performed according to a standardized maneuver by trained personnel although spirometry was not performed with reversibility test
- Residential history was not available, so exposure is only assigned for the time of inclusion into the study, which also does not take indoor or occupational air pollution into account.

INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function[1 2] and accelerated lung function decline.[3] However, evidence on specific importance of different particle sizes and sources is still limited,[4] and are to date addressed in only few epidemiological studies of respiratory health effects with non-conclusive results.[2 5 6] In panel studies, high levels of traffic PM had stronger association than total PM with short term increases in Club Cell protein CC16 (a marker of increased lung permeability) concentration in urine[7], and in controlled experiments, *in vitro* exposure of human BEAS-2B lung cells to PM from different sources triggered very different pulmonary cell and DNA damage outcomes.[8] A deepened knowledge about effects of specific particle pollution sources is thus of particular interest to prioritize public health measures to reduce health effects of ambient air pollution, and this field of research is expanding rapidly.[9]

It is only in rare cases that pollution sources be definitely identified by specific chemicals, as individual chemicals may be present in more than one source. Rather, profiles are built from particle size distributions and the relative concentrations of specific chemicals. Traffic pollution is for example characterized by NOx and ultrafine particles, whereas particles from petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and lanthanum.[10] Particles from other industry is characterized by high levels of trace metals vanadium and nickel,[10 11] but are of course sector-dependent. Similarly, PM from marine traffic is subject to large uncertainties as fuel types and fleet types vary across the world, rendering study results ungeneralizable.[12]

Beyond the importance of exposure composition and source, individual susceptibility to air pollution is modified by many factors, including genotype. Susceptibility related to genetic variability may improve our understanding of the physiological mechanisms underlying health effects of air pollution.[13 14] Glutathione S-transferase (GST) enzymes are involved in metabolizing reactive oxygen species to reduce oxidative stress.[15] GSTP1 SNPs have been reported

to modify the risk of cardiovascular disease associated with exposure to NO_2[16] and modify the association between NO_2 and lung function decline in adults,[17] but findings are inconsistent and no meta-analysis has been performed.[18] [19] Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has important functions in the innate immune system of the lungs, especially for opsonizing inhaled material.[20] SNPs in SP-A coding regions have been associated with multiple respiratory diseases,[13] [21] and suggested gene-environment interactions for smoking and chronic obstructive pulmonary disease.[22]

Many questions remain as to what components of air pollution are harmful in a general population, in particular at relatively low pollution exposures, and if such associations are modified by genetic factors. Thus, the aim of the current study was to investigate the effects of different PM sources on lung function in a general population cohort using epidemiological methods and to investigate lung function effects of genotype and gene-environment interaction with source-specific particle exposures.

METHODS

Study population

The study population originates from the ADONIX (ADult-Onset asthma and NItric oXide) cohort, a random sample of subjects aged 24-76 years who were invited to participate in a clinical examination between 2001-2008 as previously described.[16 23-26] In brief, the overall participation rate was 46%, all participants provided data on residential address, lifestyle factors and education, presence of allergic airway inflammation and respiratory health, as well as clinical

measurements of lung function, such as spirometry (single manoeuver) and nitric oxide in exhaled air (FENO). Blood samples were collected for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1 genes.

Exposure assessment

As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using dispersion modelling described in detail in Segersson and colleagues.[27] PM_{10} and $PM_{2.5}$ represent particles smaller than 10 and 2.5 micrometers (µm) respectively, whereas black carbon particles, PM_{BC}, are soot particles from combustion, notably vehicle exhaust. The specific sources were traffic (exhaust and road wear for PM_{10} and $PM_{2.5}$, exhaust only for PM_{BC}), residential heating (predominantly house heating using wood assessed as area sources), marine traffic (averaged description from a bottom-up calculation using actual positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in Gothenburg dominated by refineries, energy plants, and other industry).[28] Background concentration (long-range transport particles), was also provided, but was estimated indirectly as the difference between total modelled local contribution and monitoring data from a central urban background station. Consequently, it showed no spatial variation and was not used for analyses. To refine the estimated contribution of traffic, an increment due to reduced ventilation in the street canyons was added for the busiest streets. The increment was estimated as the difference between simulations with and without buildings using the OSPM model.[29] For each study participant's residential address at the date of clinical examination, annual mean values of pollutants were calculated separately for five source categories and modelled exposure grid values of all PM fractions were matched to the year of the participant's clinical examination.

Outcome definitions

Dynamic spirometry including FEV_1 and FVC was performed with the subject in a sitting position using a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.[30] A local reference material was used for calculation of percent predicted (% predicted) of FEV_1 and FVC and lower limit of normal, (LLN, the lower 5th percentile in healthy individuals) for FEV_1 and FVC.[31 32] Asthma was defined as reporting having had at least one asthma attack in the previous 12 months, and atopy was defined as having a positive phadiatop test. We used FEV_1, FVC and FEV_1/FVC below LLN as an indicator of clinically significant lung function reductions or air flow limitation.

Based on questionnaire replies, smoking status was categorised into current, former (no smoking during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles within residential regions, postcodes were categorised into four regions: Inner city, non-central city, suburban, and outer suburb or rural. Education was categorised in six categories: elementary school, lower secondary school, training or girls' school, grammar school, university, and "other" or not reported. Individuals who did not have information on the variables of interest were excluded, except for genotype, where analyses were run separately for each SNP. For this study we used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common) allele. Individuals with self-reported non-European background were excluded from the analysis (n=315).

Statistical methods

First, descriptive statistics were calculated for the cohort and exposure data, and correlations between the total and source-specific exposure estimates for all PM size fractions were determined.

We estimated the association between each PM size fraction for each PM source, with FEV_1 and FVC, in linear models. First, lung function effects associated with PM size fractions and sources were analysed with exposure as a continuous variable, and estimated for an interquartile increase in exposure. Second, we investigated the effects of the highest exposure values by setting high exposure cutoff for PM above the 90th percentile of population exposure, medium exposure at 50-90th percentile, with exposure at or below 50th percentile as the reference, and tested these for linear trends. To investigate clinically significant effects, we modelled increased risk of low lung function in logistic models with LLN as a cut-off. To assess confounding, covariates were added to regression models and were retained if the estimate of the main effect was altered by more than 10% by their inclusion. The covariates included in the final models were age, sex, weight, education, residential postcode region, smoking status, and exposure to passive smoking in the last 12 months. For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes and lung function for all available SNPs in single-SNP linear models. To evaluate effect modification, we tested for interaction of the effects of exposure to different PM size fractions and sources on lung function by genotype, using a likelihood ratio tests comparing the model with interaction term to the model without this term. Similarly, the analyses of PM effects were also stratified by sex and respiratory health status as well as smoking status, asthma status, atopic status, BMI, age categories to evaluate possible confounding from any of these characteristics.

All regression results for change in lung function were reported as increment or decrement in % predicted. Odds ratios were obtained from the logistic model analyses. All results are presented as point estimates with 95% confidence intervals, and with p-values as appropriate. Analyses were performed in R studio[33] using the package "phia" (post-hoc interaction analysis).[34]

RESULTS

The ADONIX cohort includes 6685 individuals, of which 5216 were included with information on the variables related to exposure and health outcomes used in this study and self-reported European ancestry. The mean age of the study population was 51.6 ±11.4 years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and 10.2% were exposed to passive smoking. A total of 9.5% of individuals had FEV_1 below lower limit of normal and 9.5% had FVC below LLN. The most common highest education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
Females	2789 (53.5%)
Respiratory health	
FEV_1 (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV_1, n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)

Below LLN of FEV_1/FVC, n (%)	548 (10.5%)
Smoking	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)
Passive smoking (last 12 months)	534 (10.2%)
Education	
Elementary school, n (%)	639 (12.2%)
Lower secondary School, n (%)	175 (3.3%)
Training/girls school, n (%)	389 (7.5%)
Grammar school, n (%)	1205 (23.1%)
University, n (%)	1954 (37.5%)
Other or not reported, n (%)	853 (16.4%)
Residential area	
Inner city, n (%)	945 (18.1%)
Non-central urban, n (%)	922 (17.7)
Suburban, n (%)	2178 (41.7%)
Outer suburb or rural, n (%)	1171 (22.4%)

*Lung function predicted from age, height and sex (Brisman et al., 2017) FEV_1, forced expiratory volume in 1 second.

FVC, forced vital capacity.

LLN, lower limit of normal, the fifth percentile of a healthy population, according to formula from Brisman et al., 2017.

The mean annual air pollution levels at the residential addresses in the study population at study entry were moderate, at 15.7 μg/m^3 PM_{10}, 9.3 μg/m^3 $PM_{2.5}$, and 0.76 μg/m^3 PM_{BC} (Table 2). Background long-range transport constituted the main source of exposure, contributing to 75% and 76% of PM_{10} and $PM_{2.5}$ levels respectively. The local emission source that contributed most to total PM_{10} was traffic, whereas residential heating contributed most to $PM_{2.5}$ (Table 2).

TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION

PM species and sources	Mean (standard deviation)	50th percentile	90th percentile	IQR
PM_{10} total	15.7 (2.49)	15.47	18.80	3.05
Traffic (μg/m^3)	2.32 (1.75)	1.78	4.41	1.64
Residential heating (μg/m^3)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m^3)	0.03 (0.05)	0.02	0.08	0.03
Industry (μg/m^3)	0.11 (0.09)	0.09	0.23	0.10
$PM_{2.5}$ total (μg/m^3)	9.33 (1.75)	9.36	11.80	2.47
Traffic (μg/m^3)	0.74 (0.56)	0.57	1.41	0.52
Residential heating (μg/m^3)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m^3)	0.03 (0.05)	0.05	0.08	0.03
Industry (μg/m^3)	0.07 (0.05)	0.06	0.12	0.06

PM_{BC} total (µg/m³)	0.76 (0.32)	0.71	1.13	0.33
Traffic (µg/m³)	0.36 (0.29)	0.27	0.69	0.25
Residential heating(µg/m³)	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (µg/m³)	0.01 (0.01)	0.00	0.02	0.01
Industry (µg/m³)	0.01 (0.01)	0.01	0.01	0.01

IQR, interquartile range.

Traffic was the largest contributor to PM_{BC}, and for PM_{BC} the contribution from long-range sources was considerably lower than for PM_{10} and $PM_{2.5}$, 26%. Traffic sources were originally divided into exhaust and road wear, but as these were highly correlated (r>0.98), we refrained from separating the two in the analyses, using instead a single variable for traffic exposure. The correlation between total and traffic-related exposure was very high for PM_{BC} (r=.99), whereas it was high for PM_{10} (r=.75) and moderate for $PM_{2.5}$ (r=.40) (Table S3).

Effects of PM exposure

Most PM sources were negatively associated with percent predicted lung function, and estimates for PM_{BC} overall and from traffic, and for $PM_{2.5}$ and PM_{10} from traffic, reached statistical significance for reductions in FEV_1 and FVC. The effect estimates for particles from residential heating, marine traffic or industry indicated no strong or consistent adverse effects in the linear models (Table 3).

TABLE 3 CHANGE IN FEV_1 AND FVC PER IQR CHANGE IN PM FROM DIFFERENT SOURCES

	Delta % predicted FEV_1				Delta % predicted FVC			
	B	95% CI			*B*	95% CI		
		Lower	Upper	p-value		Lower	Upper	p-value
PM_{10} Total	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	**-0.48**	**-0.89**	**-0.07**	**0.02**	**-0.46**	**-0.83**	**-0.08**	**0.02**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.24	0.24	1.00	-0.05	-0.27	0.17	0.66
Industry	-0.33	-0.78	0.11	0.14	-0.40	-0.80	0.01	0.05
$PM_{2.5}$ Total	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	**-0.47**	**-0.88**	**-0.07**	**0.02**	**-0.47**	**-0.83**	**-0.10**	**0.01**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
PM_{BC} Total	**-0.56**	**-1.01**	**-0.12**	**0.01**	**-0.53**	**-0.94**	**-0.13**	**0.01**
Traffic	-0.41	-0.78	-0.03	0.03	**-0.43**	**-0.77**	**-0.09**	**0.01**
Residential heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
Industry	-0.40	-0.92	0.12	0.13	-0.38	-0.85	0.09	0.11

Parameter coefficients from in separate, single-pollutant models adjusted for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

IQR, interquartile range.

In models with exposure categorized (low, medium, and high exposure), there was a consistent trend across categories for traffic-related exposure to all particulate measures for both FVC and FEV_1 (*p* for trend<0.05; for FEV_1 and PM_{BC} traffic p=0.09; the trend was slightly less strong and consistent for total exposure. There were no significant negative associations between exposure to particles of any size from residential heating, marine traffic or industrial sources and lung function (Figure 1), nor were there consistent trends (Table S4). For the odds of having FEV_1 and FVC below LLN, we observed a very similar pattern, with high exposure to all particle measures from traffic showing an increased risk of having reduced FEV_1 and FVC (p<0.05; except p=0.08 for FEV_1 and PM_{BC}) (Table S5). FEV_1/FVC below LLN was not associated with any exposure (data not shown).

Genetic main effects

The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%. (Table S1). In a main effect genetic analysis without considering environmental exposure, minor allele carrier status of three GST SNPs was associated with lung function outcomes. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV_1 reductions by -0.80% (p=0.044) and -0.90% (p=0.017), respectively, and FVC reductions were seen in minor allele carriers of the same GSTP1 SNP rs762803 (-0.74%, p=0.042) and the GSTT1 null genotype assessed with SNP rs2266637 (-1.434%, p=0.001). No main effect associations were found with SP-A SNPs (Table S1).

Effect modification of PM effects

$PM_{2.5}$, which had marginally more consistent effects for traffic-related exposure, was used for interaction analyses. The effect of genotype and exposure to $PM_{2.5}$ from all sources was analysed in interaction models, and SNPs with exposure-interaction p-values lower than 0.1 are shown in Table S2. The number of significant interactions was higher than expected by chance. The most plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV_1 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result should, however, be seen as highly exploratory. Stratifying data by smoking status, atopy, asthma status, and BMI category showed no effect modification on the estimates for air pollution effects in both linear and logistic analysis (data not shown).

DISCUSSION

In a general population cohort exposed to moderate levels of PM air pollution in a global perspective, modelled exposure to PM_{10} and $PM_{2.5}$ from traffic, as well as PM_{BC} were associated with reductions in FVC and FEV_1 in linear models, a pattern also consistently shown for high exposure in analyses with categorized exposure, and for risk of reduced FEV_1 or FVC (below LLN) in logistic regression. We observed no associations for airflow limitation (FEV_1/FVC below LLN). In this study, efforts were made to create source-specific exposure estimates, but it should be recognized that these are associated with different levels of uncertainty. Observing consistent associations between traffic-related exposure, and similar effect estimates for total exposure, but not for other sources of PM we speculate involvement of source-specific effects. However, these observations could be due to the more accurate spatial estimation of traffic, whereas the exposure estimates for both marine traffic, industry and residential heating may be less accurate.[27]

In the current study, we found the most consistent associations between both FEV_1 and FVC and traffic related particles, which is not surprising as the traffic-related pollutants with the street canyon have a higher degree of accuracy than the other pollutant sources. No obvious associations were seen between any fraction of PM from residential heating, marine traffic or industry on lung function, but their relative contribution to total PM was modest.

Although there were no associations between $PM_{2.5}$ from residential heating, marine traffic or industry on FEV_1 and FVC, we saw some exploratory but potentially interesting interaction patterns for some genotypes with industrial PM exposure, indicating that effects from industrial exposure may be less general than that of traffic particles, being concentrated within individuals with genetic susceptibilities.[13] Industrial exposure in Gothenburg is concentrated along the Götaälv river and is dominated by a power plant and oil refineries.

In spite moderate to high correlations between the three traffic related PM fractions (Table S3), total PM_{10} and $PM_{2.5}$ were not significantly associated with FVC and FEV_1, although the direction of effect was consistent with that from traffic PM_{10} and $PM_{2.5}$. Residential heating is the second largest local contribution to total PM, and we observed negative correlations between PM from residential heating and total PM as well as PM from other sources. PM from residential heating might thus be interpreted as an indicator of low exposure to other sources of air pollution which might contribute to explaining the few suggested inverse (positive) associations seen in some categorical analyses between PM from residential heating and FEV_1 and FVC (e.g. Figure 1).

In a previous study of the same cohort material, short distance to the nearest road was found to be associated with decreases in FEV_1 and FVC.[35] The pollution levels found in the current study were moderate compared to those presented in the study from Adam and colleagues.[3] In a meta-analysis of the ESCAPE data, that study found significant associations for both FEV_1 and FVC in adults related to long-term exposure to NO_2, NOx and PM_{10}, but not $PM_{2.5}$ or coarse PM. In our data, modelled annual averages of NOx and NO_2 were available for parts of the cohort for some years, and both were highly correlated with traffic PM_{10}, $PM_{2.5}$ and PM_{BC} (all correlations r>0.79).

Effects specifically of exposure to industrial emissions has not been widely studied, and industry emissions are often pooled with other sources,[27] or considered negligible as high stacks disperse the emissions.[36] Studies of respiratory health with source specific results generally find associations mainly with traffic: In the study of Jacquemin and colleagues,[7] only traffic, and not industry-specific particles were associated with the lung damage marker CC16. Krall and colleagues[9] observed only effects from tailpipe exhaust on lung function and eNO. Billet and colleagues[8] exposed cells *in-vitro* to particles from a highly industrialized environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response. Peng and colleagues[5] observed that PM from vehicle emissions, diesel engines and wood burning were associated with

the largest increases in emergency hospital admissions for CVD and respiratory disease.[5] In a multi-city European study[37] there were negative associations between FEV_1 and PM from nickel and sulphur, however results were not consistent between cities, perhaps reflecting the heterogeneity in particle compositions in different cities in the study.[38]

For the two SP-A1 SNPs that had potential interactions of interest with industry PM in our study, other studies have found rs1059057 to be associated with lung injury[39] and cystic fibrosis,[40] and rs1136451 with susceptibility to COPD,[22] but only gene-environment effects from tobacco smoking were addressed in these studies. GSTP1 SNP rs1695 was previously associated with possible increased asthma risk of air pollution exposure,[18] and we found a main effect associated with lower FEV_1 in the current study of adults. These genetic results should be seen as exploratory and be interpreted with caution.

The cohort data used in this study were collected to study respiratory health, and provides a rich dataset containing a large number of variables of interest. In the model selection, adding additional covariates as potential confounders did not affect the regression estimates substantially. Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered 2001–2003) and showed that women, the elderly, and individuals with university educated were more likely to participate.[26] As we adjusted for these covariates and as exposure was unknown to participants, this is not very likely to bias the current results.

The number of individuals who fell below the lower limit of normal for both FEV_1 and FVC was rather high, as this value is defined as the 5th percentile in a healthy, non-smoking population. It is possible that individuals with respiratory issues are more likely to take part in a study such as ADONIX. On the other hand, with clinical outcome measures and an exposure which was not known to the participants, this is an unlikely source of important bias.

In this study, complete residential histories, including duration of residence, were not available. Instead, we used a single modelled value for residential exposure that was matched by year of participation for each individual, rather than a complete longitudinal exposure history over multiple years. We consider this a reasonable approach, as the between-year correlation in air pollution concentrations and emissions in a certain location is very high.

As people spend a sizable proportion of their time outside the home, our results are based on modelled air pollution data, and thus represents an approximation of the real exposure although this is an established method. The resulting misclassification of exposure would, however, then to reduce risk estimates. The model was developed using new emissions inventories, updated information on vehicle composition, and had been further verified by measurements.[27] However, for residential heating, the source assignment is based on proxies such as building type, as no actual source inventory was available.

The very high correlations between traffic-related PM_{10}, $PM_{2.5}$ and PM_{BC} (Table S3) mean that it is difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to high correlations between the various PM source measures also meant we had to refrain from using multi-pollutant models, meaning that interpretation of estimates associated with each exposure type must be interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent associations with FEV_1 and FVC, whereas the other source-specific exposures did not.

CONCLUSION

In this large study of clinically measured outcomes in a general population sample we found that exposure to traffic particles of all three studied size fractions was associated with reductions in FEV_1 and FVC and increased risk of low FEV_1 and FVC (below LLN), supporting the need for measures to reduce urban

pollution from traffic to protect urban populations. Furthermore, we found intriguing suggestions that the SP-A1 gene may play a part in susceptibility to air pollution from industrial sources, possibly due to its very different composition.

Author contribution

HKC analysed the data and drafted the manuscript. FN and A-CO provided the cohort and genetic data, contributed to essential parts of the introduction and discussion and the final manuscript. DS provided and documented the PM exposure data. All authors approved the final version of the manuscript.

Data statement

Additional data from the ADONIX study exist and are held by the authors.

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Competing interests

None declared.

Legends

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50_{th} to 90_{th}) and high (above 90_{th} percentile) concentration of source-specific PM

Figure 2 a-e Gene-environment interactions of selected SNPs and FEV1 and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

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Supplementary tables

Table S1 Changes in FEV_1 and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs

		FEV_1				FVC			
	N (%)	*β*	95% CI Lower	Upper	p	β	95% CI Lower	Upper	*p*
GSTP									
rs1138272									
(TT+CT)	707 (14.3)								
***vs* CC**	4250 (85.7)	0.513	-0.539	1.565	0.339	0.790	-0.161	1.741	0.103
rs596603									
(TT+GT)	3363 (68.0)								
***vs* GG**	1581 (32.0)	-0.336	-1.126	0.455	0.405	-0.216	-0.931	0.499	0.554
rs762803									
(AA+AC)	3309 (67.0)								
***vs* CC**	1633 (33.0)	**-0.802**	-1.583	-0.02	**0.044**	**-0.736**	**-1.443**	**-0.028**	**0.042**
rs1695									
(AG+GG)	2683 (54.4)								
***vs* AA**	2244 (45.5)	**-0.902**	-1.643	-0.16	**0.017**	-0.575	-1.246	0.095	0.093
GSTT									
rs2266637									
GG	1005 (23.8)								
***vs* CC**	3219 (76.2)	-0.378	-1.331	0.575	0.437	**-1.431**	-2.293	-0.57	**0.001**
SP-A 1									
rs1136450									
(CC+GC)	2926 (63.8)								
***vs* GG**	1660 (36.2)	-0.106	-0.899	0.704	0.807	-0.106	-0.832	0.62	0.774
rs1136451									
(GG+GA)	1352 (29.7)								

***vs* AA**	3195 (70.3)	0.498	-0.348	1.345	0.248	0.257	-0.51	1.023	0.511
rs1059057 (GG + GA)	579 (12.6)								
***vs* AA**	4018 (87.4)	0.155	-1.003	1.313	0.793	0.073	-0.977	1.124	0.891
rs4253527 (TT+TC)	848 (18.5)								
***vs* CC**	3735 (81.5)	0.479	-0.513	1.471	0.344	0.508	-0.392	1.408	0.269
SP-A 2									
rs1059046 (GG+GT)	2814 (61.8)								
***vs* TT**	1741 (38.2)	0.070	-0.724	0.865	0.862	0.038	-0.682	0.759	0.917
rs1965707 (AA+AG)	2103 (46.2)								
***vs* GG**	2449 (53.8)	0.085	-0.686	0.856	0.829	0.255	-0.446	0.956	0.476
rs1965708) (TT+TG)	1551 (33.8)								
***vs* GG**	3041 (66.2)	-0.583	-1.397	0.231	0.160	-0.342	-1.08	0.396	0.364

With adjustment for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

Table S2 Interaction between genotype (minor allele carriers) and total and source specific PM on lung function

Gene	SNP	INTERACTION (p)* Total	Traffic	Residential heating	Marine traffic	Industry
FEV_1						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.05
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTT1	rs2266637	0. 01	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	0.04	0.01
SP-A1	rs1059057	0. 05	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	0.02	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	0.06	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	0.08	P>0.1
FVC						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.07
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	0.03
GSTT1	rs2266637	0.048	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	P>0.1	0.03
SP-A1	rs1059057	P>0.1	0.07	0.08	P>0.1	0.01
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	0.03	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	0.03	P>0.1

Interaction models were adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

Table S3 Correlation (pearson) matrix of exposure

		PM_{10}					$PM_{2.5}$					PM_{BC}				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM_{10}	Total	1														
	Traffic	0.75*	1													
	Residential heating	-0.43	-0.70*	1												
	Marine traffic	0.06	0.44	-0.83*	1											
	Industry	-0.32	0.30	-0.60*	0.63*	1										
$PM_{2.5}$	Total	0.89*	0.37	-0.12	-0.22	-0.66*	1									
	Traffic	0.77*	1*	-0.70*	0.43	0.27	0.40	1								
	Residential heating	-0.43	-0.70*	1*	-0.83*	-0.60*	-0.12	-0.70*	1							
	Marine traffic	0.06	0.44	-0.83*	1*	0.63*	-0.22	0.43	-0.83*	1						
	Industry	-0.23	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1					
PM_{BC}	Total	0.83*	0.98*	-0.59*	0.32*	0.13	0.49	0.99*	-0.59*	0.32	0.13	1				
	Traffic	0.83*	0.99*	-0.69*	0.40*	0.19	0.48	1*	-0.69*	0.40	0.21	0.99*	1			
	Residential heating	-0.41	-0.69*	1*	-0.83*	-0.62*	-0.09	-0.69*	1*	-0.83*	-0.73*	-0.58*	-0.68*	1		
	Marine traffic	0.08	0.45	-0.83*	1*	0.62*	-0.20	0.44	-0.83*	1*	0.71*	0.33	0.41	-0.83*	1	
	Industry	-0.24	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1*	0.13	0.21	-0.72*	0.70*	1

* p<0.05

Table S4 Trends in change in FEV_1 and FVC (% predicted) across exposure strata from low (0-50th percentile) to high (above 90th percentile) concentrations of source-specific PM (Figure 1)

	FEV_1				FVC			
	β	95% CI		*p*	*β*	95% CI		*p*
		Lower	Upper			Lower	Upper	
PM_{10}								
Total	-0.37	-0,97	0,22	0.22	**-0.73**	-1,27	-0,19	**0.01**
Traffic	**-0.85**	-1,51	-0,19	**0.01**	**-0.81**	-1,40	-0,21	**0.01**
Residential heating	-0.21	-0,79	0,37	0.47	0.15	-0,38	0,67	0.59
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.29	-0,91	0,33	0.36	-0.22	-0,79	0,35	0.45
$PM_{2.5}$								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	**-0.79**	-1,45	-0,13	**0.02**	**-0.81**	-1,41	-0,21	0.01
Residential heating	-0.18	-0,77	0,40	0.53	0.15	-0,37	0,68	0.57
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.12	-0,76	0,53	0.72	0.03	-0,55	0,62	0.91
PM_{BC}								
Total	**-0.66**	-1,30	-0,01	**0.05**	-0.75	-1,34	-0,17	0.01
Traffic	-0.57	-1,22	0,09	0.09	-0.75	-1,34	-0,16	0.01
Residential heating	-0.02	-0,61	0,58	0.95	0.39	-0,15	0,93	0.16
Marine traffic	0.03	-0,61	0,67	0.33	-0.34	-0,91	0,24	0.30
Industry	-0.22	-0,86	0,42	0.49	-0.03	-0,61	0,55	0.92

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

Table S5 Odds ratio of having FEV_1 and FVC below LLN in medium and high exposure strata by PM source and size fraction*

		LLN FEV_1				LLN FVC			
			95% CI				95% CI		
Model	**Percentile**	OR	**lower**	upper	p	OR	**lower**	upper	p
PM_{10}									
Total	0-50th	-	-	-	-				
	50th-90th	1.05	0.87	1.26	0.61	**1.23**	**1.00**	**1.51**	**0.05**
	90th-100th	1.18	0.86	1.62	0.31	**1.40**	**0.98**	**1.99**	**0.06**
Traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18
	90th-100th	**1.46**	**1.06**	**2.02**	**0.02**	**1.45**	**1.00**	**2.08**	**0.05**
Residential heating	0-50th	ref	-	-			ref	-	-
	50th-90th	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79
	90th-100th	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49
$PM_{2.5}$									
Total	0-50th								
	50th-90th	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77
	90th-100th	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11
Traffic	0-50th	ref	-	-	-				
	50th-90th	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09
	90th-100th	**1.47**	**1.06**	**2.03**	**0.02**	**1.54**	**1.07**	**2.21**	**0.02**
Residential heating	0-50th	ref	-	-	-	ref	-	-	
	50th-90th	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64

Industry	0-50th					ref	-	-	
	50th-90th	0.91	0.74	1.12	0.38	1.03	0.82	1.30	0.79
	90th-100th	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
PM_{BC}									
Total	0-50th					ref	-	-	
	50th-90th	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
	90th-100th	1.34	0.97	1.86	0.08	**1.46**	**1.02**	**2.09**	**0.04**
Traffic	0-50th	ref	-	-	-				
	50th-90th	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
	90th-100th	1.37	0.98	1.90	0.06	**1.55**	**1.08**	**2.23**	**0.02**
Residential heating	0-50th	ref	-	-	-	ref	-	-	
	50th-90th	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
	90th-100th	0.80	0.57	1.11	0.18	**0.64**	**0.44**	**0.94**	**0.02**
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
	90th-100th	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
Industry	0-50th					ref	-	-	
	50th-90th	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
	90th-100th	0.99	0.72	1.35	0.95	1.09	0.77	1.56	0.62

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity, LLN, lower limit of normal, the fifth percentile of a healthy population, according to formula from Brisman et al., 2017.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction pages 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, last introduction paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	In the abstract, title, and aims (last paragraph of introduction)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pages 5,6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5 and references
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Does not apply
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7, heading "outcome definitions".
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 6-7*
Bias	9	Describe any efforts to address potential sources of bias	Excluding individuals with missing data, adjusting for variables (methods, p 5-8
Study size	10	Explain how the study size was arrived at	Page 5," study population"
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 5 and 6 about exposure assessment and deinitions
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7
		(*b*) Describe any methods used to examine subgroups and interactions	Page 8
		(*c*) Explain how missing data were addressed	Page 7

		(*d*) If applicable, explain how loss to follow-up was addressed	Does not apply
		(*e*) Describe any sensitivity analyses	Page 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8, exposure page 8-9.
		(b) Indicate number of participants with missing data for each variable of interest	Does not apply
		(c) Summarise follow-up time (eg, average and total amount)	Does not apply
Outcome data	15*	Report numbers of outcome events or summary measures over time	See table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Only adjusted estimates are reported, unadjusted estimates can be provided upon request.
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Does not apply
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14, conclusions
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported on manuscript central and statements.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Exposure to traffic related particle matter and effects on lung function and potential interactions in a cross-sectional analysis of a cohort study in West Sweden

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Title page

Exposure to traffic related particle matter and effects on lung function and potential interactions in a cross-sectional analysis of a cohort study in West Sweden

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PM size fractions, PM sources, lung function, GST, SP-A, gene-environment interaction

ABSTRACT

objectives: To investigate the long-term effects of source-specific particle matter (PM) on lung function, effects of Surfactant Protein A (SP-A) and glutathione S-transferase (GST) genes GSTP1 and GSTT1 gene variants and effect modification by single nucleotide polymorphism (SNP) genotype.

design: Cohort study with address-based annual PM exposure assigned from annual estimates of size (PM_{10}, $PM_{2.5}$ and PM_{BC}) and source-specific (traffic, industry, marine traffic and wood burning) dispersion modelling.

setting: Gothenburg, Sweden.

participants: The ADONIX study had 6685 participants recruited from the general population, of which 5216 (78%) were included in the current study with information on all variables of interest. Mean age at the time of enrolment was 51.4 years (range 24-76) and 2427 (46.5%) were males.

primary and secondary outcome measures: The primary outcome was forced vital capacity (FVC) and forced expiratory flow in 1 second (FEV_1). Secondary outcome measure were effects and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

results: Exposure to traffic-related PM_{10} and $PM_{2.5}$ was associated with decreases in percent-predicted FEV_1 by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per interquartile range (IQR) 3.05 and 2.47 μg/m^3, respectively, and with decreases in percent-predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM_{BC} was strongly associated with both FEV_1 and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%) per IQR, respectively, for FVC, and similarly for FEV_1. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs showed effect modification with exposure to $PM_{2.5}$ from industry and marine traffic.

conclusions: PM exposure, specifically traffic-related, was associated with FVC and FEV_1 reductions and not modified by genotype. Genetic effect modification was suggested for industry and marine traffic $PM_{2.5}$.

Article summary: Strength and limitations of this study

- An extensive dispersion model of source-specific PM was assigned to a large, general population cohort of adults in a single urban region
- The cohort was designed with focus on respiratory health and a broad range of covariates were collected as well as genotyping for genes with known associations with respiratory health
- Spirometry was performed according to a standardized maneuver by trained personnel although not with reversibility test
- Full residential history was not available, so exposure is only assigned for the time of inclusion into the study, which also does not take indoor or occupational air pollution into account. Nevertheless, the population is known to be relatively stable and home address exposure is commonly used as the main exposure measure for air pollution since this is where people spend most of their time.

INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function[1-3] and accelerated lung function decline.[4] However, there is little evidence of the relevance of particles of different sizes and from specific sources to respiratory health on a population level.[5] To date particle sources have only been addressed in few epidemiological studies of respiratory health effects with non-conclusive results.[2 6 7] In panel studies, there were stronger associations between short term increases in Club Cell protein CC16 (a marker of increased lung permeability) concentration in urine and high levels of traffic PM than total PM.[8] In controlled experiments *in vitro,* exposing human lung cells to PM from different sources triggered very different pulmonary cell and DNA damage outcomes.[9] A deepened knowledge about effects of specific particle pollution sources is of particular interest to prioritize public health measures to reduce health effects of ambient air pollution.

In epidemiological studies, air pollution is most often assigned to certain sources by building exposure profiles from particle size distributions and relative concentrations of specific chemicals in the particles. Traffic pollution is for example characterized by NOx and ultrafine particles.[7] Particles from petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and lanthanum,[10] and particles from other industry is characterized by high levels of trace metals vanadium and nickel,[10 11] but are of course sector-dependent. Similarly, PM from marine traffic is subject to large uncertainties as fuel types and fleet types vary across the world.[12] However, this field of research is expanding rapidly as exposure science evolves with more sophisticated source specific models.[13] Beyond the importance of exposure composition and source, individual susceptibility to air pollution is modified by many factors, including genetic differences. Susceptibility related to genetic variability may improve our understanding of the physiological mechanisms underlying health effects of air pollution.[14 15] Glutathione S-transferase (GST) are involved in metabolizing reactive oxygen species to reduce oxidative stress.[16] GSTP1 SNPs have been reported to modify the risk of cardiovascular disease associated with exposure to NO_2[17] and to modify the association between NO_2 and lung function

decline in adults,[18] but findings are inconsistent and no meta-analysis has been performed.[19,20] Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has important functions in the innate immune system of the lungs, especially for opsonizing inhaled material.[21] SP-A gene polymorphisms are associated with development of serious pulmonary disease and are involved in the pulmonary defence against pathogens.[22] SNPs in SP-A coding regions have been associated with multiple respiratory diseases,[14 23] as well as gene-environment interactions for smoking and chronic obstructive pulmonary disease.[24]

Many questions remain as to what components of air pollution are harmful in a general population, in particular at relatively low pollution exposures, and if such associations are modified by genetic factors. Thus, the aim of the current study was to investigate the effects of different PM sources determined from a state-of the arts dispersion model on lung function in a general population cohort, and to investigate lung function effects of genotype and gene-environment interaction with particle exposures types.

METHODS

Study population

The study population originates from the ADONIX (ADult-Onset asthma and NItric oXide) cohort, a random sample of subjects aged 24-76 years who were invited to participate in a clinical examination between 2001-2008, as previously described.[17 25-28] In brief, the overall participation rate was 46%, all participants provided data on residential address, lifestyle factors and education, presence of allergic airway inflammation and respiratory health, as well as clinical measurements of lung function, such as spirometry (single manoeuver) and nitric oxide in exhaled air (FENO). Blood samples were collected for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1 genes.

Exposure assessment

As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using dispersion modelling described in detail by Segersson and colleagues, 2017, including a detailed map of the area.[29] PM_{10} and $PM_{2.5}$ represent particles smaller than 10 and 2.5 micrometers (µm) respectively, whereas black carbon particles, PM_{BC}, are soot particles from combustion, notably vehicle exhaust. The specific sources that were investigated were traffic (exhaust and road wear for PM_{10} and $PM_{2.5}$, exhaust only for PM_{BC}), residential heating (predominantly house heating using wood assessed as area sources), marine traffic (averaged description from a bottom-up calculation using actual positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in Gothenburg dominated by refineries, energy plants, and other industry).[30] Background concentration (long-range transport particles), was also provided, but was estimated indirectly as the difference between total modelled local contribution and monitoring data from a central urban background station. Consequently, it showed no spatial variation and was not used for analyses. To refine the estimated contribution of traffic, an increment due to reduced ventilation in street canyons was added for the busiest streets. The increment was estimated as the difference between simulations with and without buildings using the OSPM model.[31] For each study participant's residential address at the date of clinical examination, annual mean values of pollutants were calculated separately for the five source categories and modelled exposure grid values of all PM fractions were matched to the year of the participant's clinical examination.

Outcome definitions

Dynamic spirometry including FEV_1 and FVC was performed with the subject in a sitting position using a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.[32] A local reference material was used for calculation of percent predicted (% predicted) of FEV_1 and FVC and

lower limit of normal, (LLN, the lower 5th percentile in healthy individuals) for FEV_1 and FVC.[33 34] Asthma was defined as reporting having had at least one asthma attack in the previous 12 months, and atopy was defined as having a positive phadiatop test. We used FEV_1, FVC and FEV_1/FVC below LLN as an indicator of clinically significant lung function reductions or air flow limitation.

Based on questionnaire replies, smoking status was categorised into current, former (no smoking during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles within residential regions, postcodes were categorised into four residential areas: Inner city, non-central city, suburban, and outer suburb or rural. Education was categorised in six categories: elementary school, lower secondary school, training or girls' school, grammar school, university, and "other" or not reported. Individuals who did not have information on all variables of interest were excluded, except for genotype, where analyses were run separately for each SNP. For this study we used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common) allele.

Statistical methods

First, descriptive statistics were calculated for the cohort and exposure data, and correlations between the total and source-specific exposure estimates for all PM size fractions were determined.

We estimated the association between each PM size fraction for each PM source, with predicted FEV_1 and FVC, in linear models. First, percent predicted lung function effects associated with PM size fractions and sources were analysed with exposure as a continuous variable, and estimated for an interquartile increase in exposure (additionally, the analysis was repeated for lung function in Litres). Second, we investigated the effects of the highest exposure values by setting high exposure cut-off for PM above the 90th percentile of population exposure, medium exposure at 50-90th percentile, with exposure at or below 50th percentile as the reference, and tested these for linear trends. To investigate clinically significant effects, we modelled increased risk of low lung function with LLN as a cut-off in

logistic models. To assess confounding, covariates were added to regression models one at a time and were retained in the model if the coefficient of PM was altered by more than 10% by their inclusion. The covariates included in the final models were age, sex, weight, education, residential area, smoking status, and exposure to passive smoking in the last 12 months.

For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes and lung function for all available SNPs in single-SNP linear models coded as minor allele dominant effects. We present nominal p-values for these exploratory analyses. To evaluate effect modification, we tested for interaction of the effects of exposure to different PM size fractions and sources on lung function by genotype, and report the adjusted means of a fitted model adjusted for all covariate variables. The significance of the interaction terms was evaluated using a likelihood ratio tests comparing the model with interaction term to the model without this term.

In sensitivity analysis, the effects of PM were analysed in models stratified by sex, smoking status, asthma status, atopic status, BMI categories, and age categories to evaluate possible confounding from any of these characteristics.

All regression results for change in lung function were reported as increment or decrement in % predicted. Change in mL is reported in the supplement. Odds ratios were obtained from the logistic model analyses. All results are presented as point estimates with 95% confidence intervals, and with p-values as appropriate. Analyses were performed in R studio.[35]

RESULTS

The ADONIX cohort includes 6685 individuals. After excluding individuals with missing data on explanatory variables such as smoking status (25), environmental tobacco smoke (76), and who had missing, or very low quality of lung function (532), there were 6006 individuals, further 333 had a missing postcode, 315 did not have a European background, and 457 were outside the catchment area leaving 5216 for the main analysis. In the genetic analysis, up to 276 individuals had missing data.

Finally, 5216 were included with information on the variables related to exposure and health outcomes used in this study and self-reported European ancestry. The mean age of the study population was 51.6 ±11.4 years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and 10.2% were exposed to passive smoking. A total of 12.6% (n=656) of the study population had FEV_1 below lower limit of normal and 9.5% (n=494) had FVC below LLN. The most common highest education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
Females	2789 (53.5%)
Respiratory health	
FEV_1 (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV_1, n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV_1/FVC, n (%)	548 (10.5%)
Smoking	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)
Passive smoking (last 12 months)	534 (10.2%)
Education	

Elementary school, n (%)	639 (12.2%)
Lower secondary School, n (%)	175 (3.3%)
Training/girls school, n (%)	389 (7.5%)
Grammar school, n (%)	1205 (23.1%)
University, n (%)	1954 (37.5%)
Other or not reported, n (%)	853 (16.4%)
Residential area	
Inner city, n (%)	945 (18.1%)
Non-central urban, n (%)	922 (17.7)
Suburban, n (%)	2178 (41.7%)
Outer suburb or rural, n (%)	1171 (22.4%)
Self-reported respiratory health**	
Current asthma, n (%)	462/4698 (9.0%)
MD diagnosed asthma, n (%)	348/4828 (6.9%)
Allergy***, n (%)	1220/3887 (23.9%)
BMI, mean (standard deviation)	26.1 (4.1)

*Lung function predicted from age, height and sex.[33] FEV_1, forced expiratory volume in 1 second. FVC, forced vital capacity. LLN, lower limit of normal, the fifth percentile of a healthy population.

**Adapted from questionnaire data asking about, have you had an asthma attack in the last 12 months,

***Allergy was determined by a positive phadiatop test (IgE >0.35 IU/mL)

193 The mean annual air pollution levels at the residential addresses in the study population at study entry
194 were moderate, at 15.7 µg/m^3 PM_{10}, 9.3 µg/m^3 $PM_{2.5}$, and 0.76 µg/m^3 PM_{BC} (Table 2). Background long-

range transported particle matter constituted the larger proportion of exposure, contributing t75% and 76% of the total PM_{10} and $PM_{2.5}$ levels, respectively. The local emission source that contributed mostly to total PM_{10} was traffic, whereas residential heating contributed most to $PM_{2.5}$ (Table 2).

TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION

PM species and sources	Mean (SD)	50th percentile	90th percentile	IQR
PM_{10} total	15.7 (2.49)	15.47	18.80	3.05
Traffic (µg/m³)	2.32 (1.75)	1.78	4.41	1.64
Residential heating (µg/m³)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (µg/m³)	0.03 (0.05)	0.02	0.08	0.03
Industry (µg/m³)	0.11 (0.09)	0.09	0.23	0.10
$PM_{2.5}$ total (µg/m³)	9.33 (1.75)	9.36	11.80	2.47
Traffic (µg/m³)	0.74 (0.56)	0.57	1.41	0.52
Residential heating (µg/m³)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (µg/m³)	0.03 (0.05)	0.05	0.08	0.03
Industry (µg/m³)	0.07 (0.05)	0.06	0.12	0.06
PM_{BC} total (µg/m³)	0.76 (0.32)	0.71	1.13	0.33
Traffic (µg/m³)	0.36 (0.29)	0.27	0.69	0.25
Residential heating(µg/m³)	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (µg/m³)	0.01 (0.01)	0.00	0.02	0.01
Industry (µg/m³)	0.01 (0.01)	0.01	0.01	0.01

IQR, interquartile range. SD, standard deviation.

Traffic was the largest contributor to PM_{BC}, and for PM_{BC} the contribution from long-range sources was considerably lower than for PM_{10} and $PM_{2.5}$, at 26%. Traffic sources were originally divided into exhaust

and road wear, but as these were highly correlated (r>0.98) we combined the two into a single variable for traffic exposure and used that in the analyses. The correlation between total and traffic-related exposure was very high for PM_{BC} (r=0.99), whereas it was high for PM_{10} (r=0.75) and moderate for $PM_{2.5}$ (r=.040) (Table S1).

Effects of PM exposure

Percent predicted lung function were negatively associated with PM_{10} and $PM_{2.5}$ from traffic, and with PM_{BC} in linear models with continuous exposure. The effect estimates for particles from residential heating, marine traffic or industry indicated no strong or consistent adverse effects in the linear models (Table 3).

TABLE 3 ESTIMATED CHANGE IN FEV_1 AND FVC PER IQR CHANGE IN PM FROM DIFFERENT SOURCES

	Delta % predicted FEV_1				Delta % predicted FVC			
	B	95% CI			*B*	95% CI		
		Lower	Upper	p-value		Lower	Upper	p-value
PM_{10} Total	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	**-0.48**	**-0.89**	**-0.07**	**0.02**	**-0.46**	**-0.83**	**-0.08**	**0.02**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.24	0.24	1.00	-0.05	-0.27	0.17	0.66
Industry	-0.33	-0.78	0.11	0.14	-0.40	-0.80	0.01	0.05
$PM_{2.5}$ Total	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	**-0.47**	**-0.88**	**-0.07**	**0.02**	**-0.47**	**-0.83**	**-0.10**	**0.01**

Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
PM_{BC} Total	**-0.56**	**-1.01**	**-0.12**	**0.01**	**-0.53**	**-0.94**	**-0.13**	**0.01**
Traffic	**-0.41**	**-0.78**	**-0.03**	**0.03**	**-0.43**	**-0.77**	**-0.09**	**0.01**
Residential heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
Industry	-0.40	-0.92	0.12	0.13	-0.38	-0.85	0.09	0.11

Parameter coefficients from in separate, single-pollutant models adjusted for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

IQR, interquartile range.

In models with categorical exposure (low, medium, and high exposure), there was a consistent trend across categories for traffic-related exposure in all particulate measures for both percent predicted FVC and FEV_1 (*p* for trend<0.05; for FEV_1 and PM_{BC} traffic p=0.09); the trend was slightly less strong and consistent for total PM exposure (Figure 1). There were no significant negative associations between percent predicted lung function and exposure to particles of any size from residential heating, marine traffic or industrial sources (Figure 1), nor were there statistically significant trends (Table S2). Estimating effects on lung function in mL rather than % predicted we observed significant decreases of FEV_1 and FVC associated with PM_{10} traffic, $PM_{2.5}$ total and traffic as in the percent predicted analysis (Table S3 and Table 3). However, in this analysis PM_{10} and PM_{BC} from industry were also associated with decreased FEV_1 and FVC (Table S3). In a logistic regression, high exposure to any particle fraction

from traffic were associated with increased odds ratio of having clinically significant reductions in FEV_1 and FVC (below LLN) ($p<0.05$; except $p=0.08$ for FEV_1 and PM_{BC}) (Table S4). The ratio FEV_1/FVC below LLN was not associated with any exposure (data not shown).

Genetic main effects

All SNPs were in Hardy-Weinberg equilibrium except rs1136450, which has one very rare genotype (n=12). The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%. (Table S5). In a main effect analysis without considering environmental exposure, minor allele carrier status of three GST SNPs was associated with lung function outcomes in minor allele dominant genetic models. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV_1 reductions by -0.80% (p=0.044) and -0.90% (p=0.017), respectively, and FVC reductions were seen in minor allele carriers of the same GSTP1 SNP rs762803 (-0.74%, p=0.042) and the GSTT1 null genotype assessed with SNP rs2266637 (-1.434%, p=0.001). No main effect associations were found with SP-A SNPs (Table S5).

Effect modification of PM effects

$PM_{2.5}$, which had marginally more consistent effects for traffic-related exposure, was used for exploratory interaction analyses. The effect of genotype and exposure to $PM_{2.5}$ from all sources was analysed in interaction models, and SNPs with exposure-interaction p-values below 0.1 are shown in Table S6. The number of significant interactions was higher than expected by chance. The most plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV_1 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result should, however, be seen as highly exploratory. Stratifying data by smoking status, atopy, asthma status, and BMI category showed no significant effect modification on the estimates for air pollution effect on lung function in either linear or logistic analysis (data not shown).

DISCUSSION

In a general population cohort we observed significant associations between lung function and modelled exposure to PM_{10} and $PM_{2.5}$ from traffic as well as PM_{BC}. The association between FEV_1 and FVC was consistently present in 1) linear models with continuous exposure (Table 3) , and 2) in models in which exposure was expressed as categories, high exposure (above the 90th percentile) compared to low exposure (<50th percentile) with significant trends across three exposure strata (Figure 1, Table S2). In the analyses, the observed average decreases were numerically small and without individual-level clinical significance, but in logistic regression models with binary outcomes, FEV_1 below LLN was associated with high exposure to PM_{10} and $PM_{2.5}$ traffic particles, and FVC below LLN was associated with traffic particles in all size fractions as well as total PM_{BC} (Table S4). This pattern was also found when exposure was expressed categorically for a continuous outcome (Figure 1). We observed no associations with airflow limitation, rather the negative associations with exposure means that such effects, which could possibly explained by the parallel reduction of both FEV_1 and FVC.

Because we observed significant associations between percent predicted lung function and most traffic-related exposure metrics on a population level, and no obvious associations were found between any fractions of PM from residential heating, marine traffic or industry, our results indicate that exposure to PM from traffic is particularly detrimental to lung function. However, we cannot rule out that we observed the lack of associations to other sources were due to a lower accuracy in exposure assessment for these sources. Furthermore, the relative contribution of marine traffic, industry and residential heating to total PM was modest (Table 2), which could also lead to inaccurate or low estimates without statistical significance. There are hypotheses postulating that exposure to newly formed particles, such as from traffic close to the domestic address, may be more potent and reactive, but so far there seem to be no consensus.[29 36] Interestingly, in the analysis of crude lung function (in mL, rather than percent of predicted) we also observed associations with particles of

industrial origin, suggesting that they could be modified by factors related to age, height and sex which are accounted for in the percent predicted value.

In spite of there being moderate to high correlations (0.75, 0.42 and 0.99) between total PM and traffic related PM in any of the three fractions (Table S1), total PM_{10} and $PM_{2.5}$ were not significantly associated with reductions in percent predicted FVC and FEV_1. Residential heating is the second largest local contribution to total PM, and we observed negative correlations between PM from residential heating and total PM as well as PM from other sources. PM from residential heating could thus be interpreted as an indicator of low exposure to other sources of air pollution which might contribute to explaining the few suggested inverse (positive) associations seen in some categorical analyses between PM from residential heating and FEV_1 and FVC (e.g. Figure 1).

For GSTP and GSTT genotypes, where carrying the minor or null allele, were associated with decreased percent predicted FEV_1 and FVC, whereas no direct effects of SP-ASNPS were found (Table S4). Gene-environment interactions were tested for all SNPs and all PM sources and size fraction, but significant and biologically plausible interactions were only observed between specific SP-A SNPs and exposure to $PM_{2.5}$ from marine traffic and industrial sources, and not for traffic or total PM, where most direct effects where observed. We thus infer that it is possible that detrimental effects from marine traffic and industry PM t may affect specific individuals with genetic susceptibilities.[14] Industrial exposure in Gothenburg is concentrated along the northern mouth of the Göta Älv River and is dominated by a power plant and oil refineries. PM from marine traffic is also concentrated along the river.

During initial analysis and covariate selection, we found that residential region was an effect modifier, and included this as a covariate in the study. Other studies of lung function within a single region have adjusted for municipality to avoid confounding of the results which is likely due socio-economic distribution of the study population in some urban areas, where high-exposed areas also have a high proportion of individuals with high socio-economic status which entails other risk factor panorama and health behaviours.[37]

In a previous study on the same cohort population, short distance to the nearest road was found to be associated with decreases in FEV_1 and FVC.[38] Comparing with other studies, the size of the estimated change in lung function in our study are similar and within confidence intervals of those reported from the UK biobank.[3] The pollution levels found in the current study were moderate compared to those presented in the study from Adam and colleagues, reporting significant associations for both FEV_1 and FVC in adults related to long term exposure to NO_2, NOx and PM_{10}, but not $PM_{2.5}$ or coarse PM in a meta-analysis of the ESCAPE data.[7] In our study, both of NOx and NO_2 were highly correlated with traffic PM_{10}, $PM_{2.5}$ and PM_{BC} (all correlations r>0.79), for the years that both NOx and NO_2 and source specific PM estimates were available.

Effects specifically of exposure to industrial emissions have not been widely studied, and industry emissions are often pooled with other sources,[29] or considered negligible as high stacks disperse the emissions.[39] Studies of respiratory health with source specific results generally find associations mainly with traffic: In the study of Jacquemin and colleagues,[8] only traffic, and not industry-specific particles were associated with the lung damage marker CC16. Krall and colleagues[13] observed only effects from tailpipe exhaust on lung function and eNO. Billet and colleagues[9] exposed cells *in-vitro* to particles from a highly industrialized environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response. Peng and colleagues[6] observed that PM from vehicle emissions, diesel engines and wood burning were associated with the largest increases in emergency hospital admissions for CVD and respiratory disease.[6] In a multi-city European study[40] there were negative associations between FEV_1 and PM from nickel and sulphur, however results were not consistent between cities, perhaps reflecting the heterogeneity in particle compositions in different cities in the study.[41]

SP-A has the ability to bind and help clear pathogens but also particle matter from the lungs by opsonisation[22] and is activated in response to exposure to Ozone, another major air pollutant[42] Previous literature suggest that SNPs of SP-A are associated with defect opsonisation, and hence

increased risk for viral infections,[43] but likely also for adverse effects of particle exposure (as well as volatile exposures.[22] We found a significant interaction between polymorphisms of two SP-A1 SNPs and the association between exposure to PM from industrial sources and lung function. Other studies have found rs1059057 to be associated with acute lung injury[22] and cystic fibrosis,[44] and rs1136451 with susceptibility to COPD and analysed gene-environment effects from tobacco smoking.[24] The SP-A 2 SNP rs4253527 has been associated with tuberculosis.[22]

We observed no gene-environment interactions with any GSTT or GSTP SNPS. The GSTP SNP rs1695 has been associated with possible increased asthma risk of air pollution exposure,[19] whereas we found a main effect with lower FEV_1 in the current study of adults, but no interactions. These genetic interactions results should be seen as exploratory and be interpreted with caution.

Strengths and limitations

The cohort data used in this study were collected to study respiratory health, and provides a rich dataset containing a large number of variables of interest. In the model selection, adding additional covariates as potential confounders did not affect the regression estimates substantially. Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered 2001–2003) and showed that women, the elderly, and individuals with university education were more likely to participate.[28] As we adjusted for these covariates and as exposure was unknown to participants, this is not likely to bias the current results.

The number of individuals who fell below the lower limit of normal for both FEV_1 and FVC was rather high, as this value is defined as the 5^{th} percentile in a healthy, non-smoking population. It is possible that individuals with respiratory issues, as well as past and present smokers, are more likely to take part in a study such as ADONIX.[28] On the other hand, with clinical outcome measures and an exposure which was not known to the participants, this is an unlikely source of important bias.

In this study, complete residential histories, including duration of residence, were not available. Instead, we used a single modelled value for residential exposure that was matched by year of

participation for each individual, rather than a complete longitudinal exposure history over multiple years. We consider this a reasonable approach, as the between-year correlation in air pollution concentrations and emissions in a certain location is very high.

As people spend a fair proportion of their time outside their home, and our results are based on modelled air pollution data at the place of residence, the exposure represents an approximation of the real exposure. However, this is an established method which provides a fair picture of the actual exposure. The resulting, and likely nondifferential, misclassification of exposure would, however, then to shrink risk estimates towards the null. The model was developed using new emissions inventories, updated information on vehicle composition, and had been further verified by measurements.[29] However, for residential heating, the source assignment is based on proxies such as building type, as no actual source inventory was available, and may have a poorer performance.

The very high correlations between traffic-related PM_{10}, $PM_{2.5}$ and PM_{BC} (Table S1) mean that it is difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to high correlations between the various PM source measures also meant we had to refrain from using multi-pollutant models, meaning that f estimates associated with each exposure type must be interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent associations with FEV_1 and FVC, whereas the other source-specific exposures did not.

CONCLUSION

In this large study of clinically measured outcomes in a general population sample we found that exposure to traffic particles of all three studied PM species and size fractions were associated with reductions in FEV_1 and FVC and increased risk of low FEV_1 and FVC (below LLN), supporting the need for measures to reduce urban pollution from traffic to protect urban populations. Furthermore, we found intriguing suggestions in our exploratory analysis that the SP-A1 gene may play a part in susceptibility to air pollution from industrial sources, possibly due to its very different composition.

Author Contributions

HKC analysed the data and drafted the manuscript. FN, KT, and A-CO provided the cohort and genetic data, contributed to essential parts of the introduction and discussion and the final manuscript. DS provided and documented the PM exposure data. All authors approved the final version of the manuscript and contributed to the discussion.

Data statement

Additional data from the ADONIX study exist and are held by the authors.

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Competing interests

None declared.

Ethics approval: The Västra Götaland Region ethical review board approved of the study (ref no. Ö 092-01) and participants gave informed consent.

Legends

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50_{th} to 90_{th}) and high (above 90_{th} percentile) concentration of source-specific PM

Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV_1 and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

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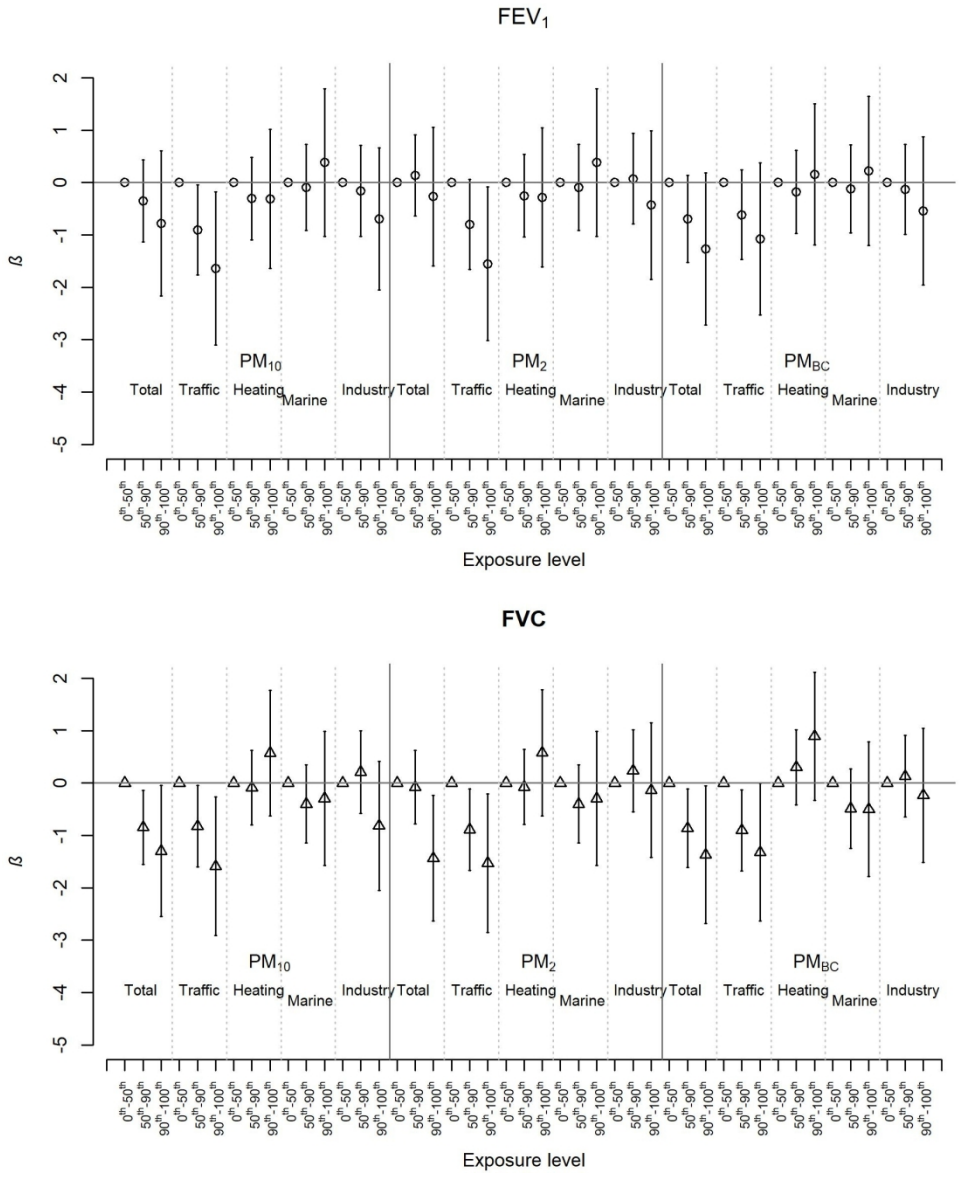

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

169x203mm (300 x 300 DPI)

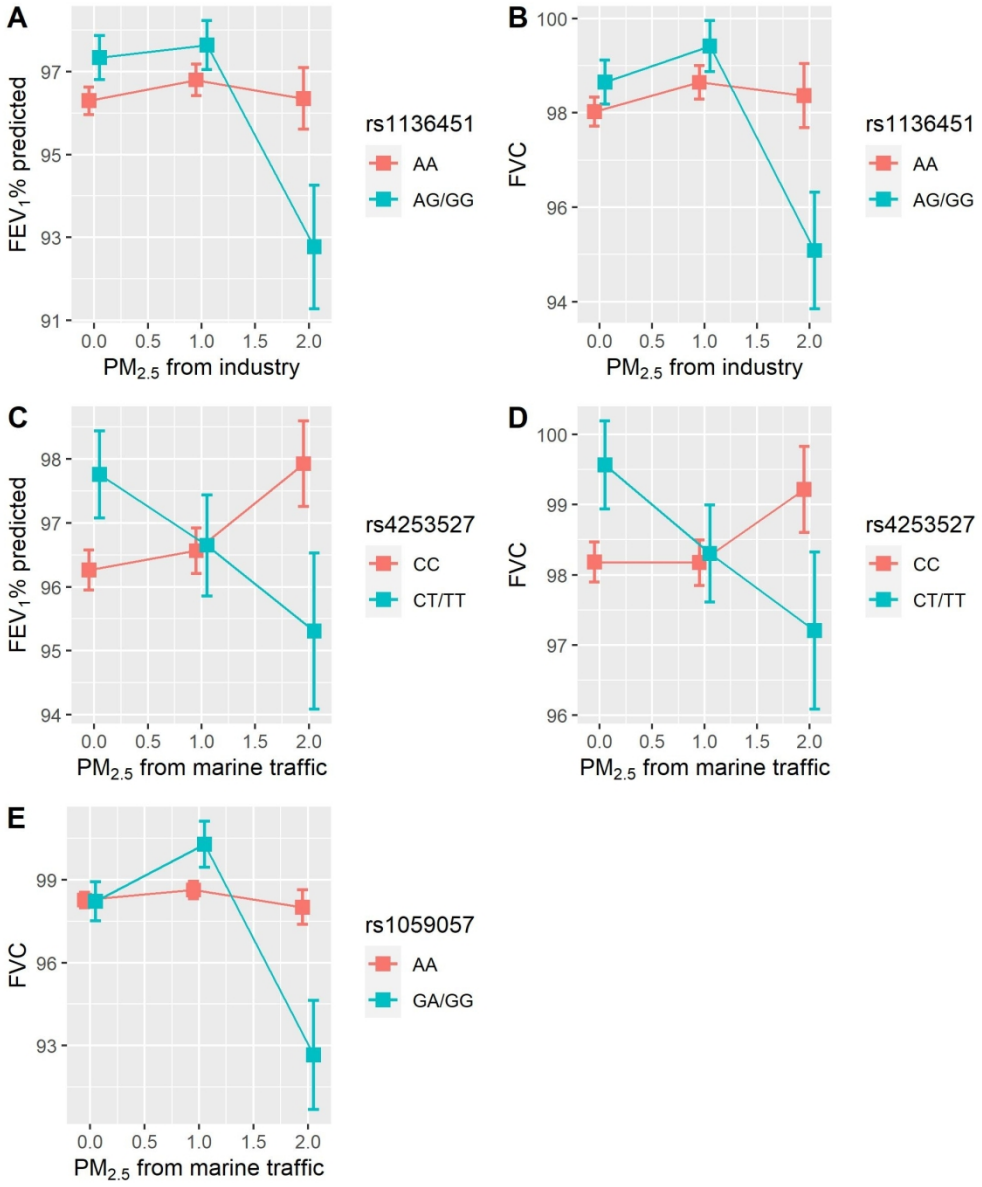

Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV_1 and FVC in exposure categories to select PM sources with standard error bars. Dotted lines represent effects on minor allele carriers

169x203mm (300 x 300 DPI)

Table S1 Correlation (Pearson's) matrix of exposure

		PM_{10}					$PM_{2.5}$					PM_{BC}				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM_{10}	Total	1														
	Traffic	0.75*	1													
	Residential heating	-0.43	-0.70*	1												
	Marine traffic	0.06	0.44	-0.83*	1											
	Industry	-0.32	0.30	-0.60*	0.63*	1										
$PM_{2.5}$	Total	0.89*	0.37	-0.12	-0.22	-0.66*	1									
	Traffic	0.77*	1*	-0.70*	0.43	0.27	0.40	1								
	Residential heating	-0.43	-0.70*	1*	-0.83*	-0.60*	-0.12	-0.70*	1							
	Marine traffic	0.06	0.44	-0.83*	1*	0.63*	-0.22	0.43	-0.83*	1						
	Industry	-0.23	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1					
PM_{BC}	Total	0.83*	0.98*	-0.59*	0.32*	0.13	0.49	0.99*	-0.59*	0.32	0.13	1				
	Traffic	0.83*	0.99*	-0.69*	0.40*	0.19	0.48	1*	-0.69*	0.40	0.21	0.99*	1			
	Residential heating	-0.41	-0.69*	1*	-0.83*	-0.62*	-0.09	-0.69*	1*	-0.83*	-0.73*	-0.58*	-0.68*	1		
	Marine traffic	0.08	0.45	-0.83*	1*	0.62*	-0.20	0.44	-0.83*	1*	0.71*	0.33	0.41	-0.83*	1	
	Industry	-0.24	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1*	0.13	0.21	-0.72*	0.70*	1

* $p<0.05$

Supplementary tables for ADONIX: Lung function and source specific PM

Table S2 Trends in change in FEV_1 and FVC (% predicted) across exposure strata from low (0-50th percentile) to high (above 90th percentile) concentrations of source-specific PM (Figure 1)

	FEV_1				FVC			
	β	95% CI		*p*	*β*	95% CI		*p*
		Lower	Upper			Lower	Upper	
PM_{10}								
Total	-0.37	-0,97	0,22	0.22	**-0.73**	-1,27	-0,19	**0.01**
Traffic	**-0.85**	-1,51	-0,19	**0.01**	**-0.81**	-1,40	-0,21	**0.01**
Residential heating	-0.21	-0,79	0,37	0.47	0.15	-0,38	0,67	0.59
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.29	-0,91	0,33	0.36	-0.22	-0,79	0,35	0.45
$PM_{2.5}$								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	**-0.79**	-1,45	-0,13	**0.02**	**-0.81**	-1,41	-0,21	0.01
Residential heating	-0.18	-0,77	0,40	0.53	0.15	-0,37	0,68	0.57
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.12	-0,76	0,53	0.72	0.03	-0,55	0,62	0.91
PM_{BC}								
Total	**-0.66**	-1,30	-0,01	**0.05**	-0.75	-1,34	-0,17	0.01
Traffic	-0.57	-1,22	0,09	0.09	-0.75	-1,34	-0,16	0.01
Residential heating	-0.02	-0,61	0,58	0.95	0.39	-0,15	0,93	0.16
Marine traffic	0.03	-0,61	0,67	0.33	-0.34	-0,91	0,24	0.30
Industry	-0.22	-0,86	0,42	0.49	-0.03	-0,61	0,55	0.92

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

Supplementary tables for ADONIX: Lung function and source specific PM

Table S3 Change in FEV_1 and FVC (mL) per IQR change in PM exposure

		FEV1			FVC		
			95% CI			95% CI	
	IQR (µg/m³)	*β*	*Lower*	*Upper*	*β*	*Lower*	*Upper*
PM_{10}							
Total	3.05	-23	-46	0	-11	-30	8
Traffic	1.64	**-23**	**-43**	**-4**	**-20**	**-36**	**-4**
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-8	16	4	-6	13
Industry	0.10	**-26**	**-47**	**-5**	**-18**	**-35**	**-1**
$PM_{2.5}$							
Total	2.47	**-28**	**-54**	**-3**	-5	-26	15
Traffic	0.52	**-24**	**-43**	**-5**	**-20**	**-36**	**-4**
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-38	46	4	-30	38
Industry	0.06	**-24**	**-49**	**0**	**-18**	**-38**	**2**
PM_{BC}							
Total	0.33	**-29**	**-50**	**-8**	**-25**	**-42**	**-7**
Traffic	0.25	**-24**	**-42**	**-6**	**-18**	**-33**	**-4**
Residential heating	0.07	4	-21	28	-11	-31	8
Marine traffic	0.01	3	-8	15	3	-6	13
Industry	0.01	**-27**	**-51**	**-2**	**-20**	**-40**	**0**

Change estimated from linear regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months

Supplementary tables for ADONIX: Lung function and source specific PM

Table S4 Odds ratio of having FEV_1 and FVC below LLN in medium and high exposure strata by PM source and size fraction*

		LLN FEV_1				LLN FVC			
			95% CI				95% CI		
Model	**Percentile**	OR	**lower**	upper	p	OR	**lower**	upper	p
PM_{10}									
Total	0-50th	-	-	-	-				
	50th-90th	1.05	0.87	1.26	0.61	**1.23**	**1.00**	**1.51**	**0.05**
	90th-100th	1.18	0.86	1.62	0.31	**1.40**	**0.98**	**1.99**	**0.06**
Traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18
	90th-100th	**1.46**	**1.06**	**2.02**	**0.02**	**1.45**	**1.00**	**2.08**	**0.05**
Residential heating	0-50th	ref	-	-			ref	-	-
	50th-90th	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79
	90th-100th	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49
$PM_{2.5}$									
Total	0-50th								
	50th-90th	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77
	90th-100th	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11
Traffic	0-50th	ref	-	-	-				
	50th-90th	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09
	90th-100th	**1.47**	**1.06**	**2.03**	**0.02**	**1.54**	**1.07**	**2.21**	**0.02**
Residential heating	0-50th	ref	-	-	-	ref	-	-	
	50th-90th	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50th					ref	-	-	
	50th-90th	0.91	0.74	1.12	0.38	1.03	0.82	1.30	0.79

Supplementary tables for ADONIX: Lung function and source specific PM

	90^{th}-100^{th}	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
PM_{BC}									
Total	0-50^{th}					ref	-	-	
	50^{th}-90^{th}	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
	90^{th}-100^{th}	1.34	0.97	1.86	0.08	**1.46**	**1.02**	**2.09**	**0.04**
Traffic	0-50^{th}	ref	-	-	-				
	50^{th}-90^{th}	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
	90^{th}-100^{th}	1.37	0.98	1.90	0.06	**1.55**	**1.08**	**2.23**	**0.02**
Residential heating	0-50^{th}	ref	-	-	-	ref	-	-	
	50^{th}-90^{th}	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
	90^{th}-100^{th}	0.80	0.57	1.11	0.18	**0.64**	**0.44**	**0.94**	**0.02**
Marine traffic	0-50^{th}	ref	-	-		ref	-	-	
	50^{th}-90^{th}	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
	90^{th}-100^{th}	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
Industry	0-50^{th}					ref	-	-	
	50^{th}-90^{th}	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
	90^{th}-100^{th}	0.99	0.72	1.35	0.95	1.09	0.77	1.56	0.62

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity, LLN, lower limit of normal, the fifth percentile of a healthy population, according to formula from Brisman et al., 2017.

Table S5 Genetic main effects: Changes in FEV_1 and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs

		FEV_1				FVC			
	N (%)	*β*	95% CI Lower	Upper	p	β	95% CI Lower	Upper	*p*
GSTP									
rs1138272									
(TT+CT)	707 (14.3)								
***vs* CC**	4250 (85.7)	0.513	-0.539	1.565	0.339	0.790	-0.161	1.741	0.103
rs596603									
(TT+GT)	3363 (68.0)								
***vs* GG**	1581 (32.0)	-0.336	-1.126	0.455	0.405	-0.216	-0.931	0.499	0.554
rs762803									
(AA+AC)	3309 (67.0)								
***vs* CC**	1633 (33.0)	**-0.802**	**-1.583**	**-0.02**	**0.044**	**-0.736**	**-1.443**	**-0.028**	**0.042**
rs1695									
(AG+GG)	2683 (54.4)								
***vs* AA**	2244 (45.5)	**-0.902**	**-1.643**	**-0.16**	**0.017**	-0.575	-1.246	0.095	0.093
GSTT									
rs2266637									
GG	1005 (23.8)								
***vs* CC**	3219 (76.2)	-0.378	-1.331	0.575	0.437	**-1.431**	**-2.293**	**-0.57**	**0.001**
SP-A 1									
rs1136450									
(CC+GC)	2926 (63.8)								
***vs* GG**	1660 (36.2)	-0.106	-0.899	0.704	0.807	-0.106	-0.832	0.62	0.774
rs1136451									
(GG+GA)	1352 (29.7)								
***vs* AA**	3195 (70.3)	0.498	-0.348	1.345	0.248	0.257	-0.51	1.023	0.511
rs1059057									
(GG + GA)	579 (12.6)								
***vs* AA**	4018 (87.4)	0.155	-1.003	1.313	0.793	0.073	-0.977	1.124	0.891
rs4253527									

(TT+TC)	848 (18.5)								
***vs* CC**	3735 (81.5)	0.479	-0.513	1.471	0.344	0.508	-0.392	1.408	0.269
SP-A 2									
rs1059046									
(GG+GT)	2814 (61.8)								
***vs* TT**	1741 (38.2)	0.070	-0.724	0.865	0.862	0.038	-0.682	0.759	0.917
rs1965707									
(AA+AG)	2103 (46.2)								
***vs* GG**	2449 (53.8)	0.085	-0.686	0.856	0.829	0.255	-0.446	0.956	0.476
rs1965708)									
(TT+TG)	1551 (33.8)								
***vs* GG**	3041 (66.2)	-0.583	-1.397	0.231	0.160	-0.342	-1.08	0.396	0.364

With adjustment for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

Table S6 Interaction between genotype (minor allele carriers) and total and source specific PM on lung function in a linear model

Gene	SNP	INTERACTION (p)* Total	Traffic	Residential heating	Marine traffic	Industry
FEV_1						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.05
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTT1	rs2266637	0. 01	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	**0.04**	**0.01**
SP-A1	rs1059057	0. 05	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	**0.02**	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	0.06	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	0.08	P>0.1
FVC						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.07
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	**0.03**
GSTT1	rs2266637	0.048	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	P>0.1	0.03
SP-A1	rs1059057	P>0.1	0.07	0.08	P>0.1	**0.01**
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	**0.03**	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	**0.03**	P>0.1

Interaction models were adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok,
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction pages 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, last introduction paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	In the abstract, title, and aims (last paragraph of introduction)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods line 102,
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Line 102 and and references therein
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Does not apply
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	From line 133
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*From line 102 (cohort) and line 111 (exposure)*
Bias	9	Describe any efforts to address potential sources of bias	See statistical methods
Study size	10	Explain how the study size was arrived at	From line 103
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	From line 132
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	From line 154
		(*b*) Describe any methods used to examine subgroups and interactions	Line 171 and 173
		(*c*) Explain how missing data were addressed	Lines 281-286
		(*d*) If applicable, explain how loss to follow-up was addressed	Does not apply
		(*e*) Describe any sensitivity analyses	Line 173-175.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	Line 281-286.

		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8, exposure page 8-9.
		(b) Indicate number of participants with missing data for each variable of interest	Does not apply
		(c) Summarise follow-up time (eg, average and total amount)	Does not apply
Outcome data	15*	Report numbers of outcome events or summary measures over time	See table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Adjusted estimates are reported as main results, unadjusted estimates can be provided upon request. Interaction results are reported without adjustment.
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Does not apply
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Line 244-246.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Line 248 onwards.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See article summary, from line 50, and in discussion line 331 onward
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion and interpretation lines 253 and onwards. Results from similar studies lines 291-316.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 364 onward
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported on manuscript central and statements.

*Give information separately for exposed and unexposed groups.

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Exposure to traffic related particle matter and effects on lung function and potential interactions in a cross-sectional analysis of a cohort study in West Sweden

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Title page

Exposure to traffic related particle matter and effects on lung function and potential interactions in a cross-sectional analysis of a cohort study in West Sweden

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PM size fractions, PM sources, lung function, GST, SP-A, gene-environment interaction

ABSTRACT

objectives: To investigate the long-term effects of source-specific particle matter (PM) on lung function, effects of Surfactant Protein A (SP-A) and glutathione S-transferase (GST) genes GSTP1 and GSTT1 gene variants and effect modification by single nucleotide polymorphism (SNP) genotype.

design: Cohort study with address-based annual PM exposure assigned from annual estimates of size (PM_{10}, $PM_{2.5}$ and PM_{BC}) and source-specific (traffic, industry, marine traffic and wood burning) dispersion modelling.

setting: Gothenburg, Sweden.

participants: The ADONIX study had 6685 participants recruited from the general population, of which 5216 (78%) were included in the current study with information on all variables of interest. Mean age at the time of enrolment was 51.4 years (range 24-76) and 2427 (46.5%) were males.

primary and secondary outcome measures: The primary outcome was forced vital capacity (FVC) and forced expiratory flow in 1 second (FEV_1). Secondary outcome measure were effects and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

results: Exposure to traffic-related PM_{10} and $PM_{2.5}$ was associated with decreases in percent-predicted FEV_1 by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per interquartile range (IQR) 3.05 and 2.47 μg/m^3, respectively, and with decreases in percent-predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM_{BC} was strongly associated with both FEV_1 and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%) per IQR, respectively, for FVC, and similarly for FEV_1. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs showed effect modification with exposure to $PM_{2.5}$ from industry and marine traffic.

conclusions: PM exposure, specifically traffic-related, was associated with FVC and FEV_1 reductions and not modified by genotype. Genetic effect modification was suggested for industry and marine traffic $PM_{2.5}$.

Article summary: Strength and limitations of this study

- An extensive dispersion model of source-specific PM was assigned to a large, general population cohort of adults in a single urban region
- The cohort was designed with focus on respiratory health and a broad range of covariates were collected as well as genotyping for genes with known associations with respiratory health
- Spirometry was performed according to a standardized maneuver by trained personnel although not with reversibility test
- A full residential history was not available and thus exposure was assigned for the time of the participation and indoor or occupational air pollution exposure was not taken into account."

INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function[1-3] and accelerated lung function decline.[4] However, there is little evidence of the relevance of particles of different sizes and from specific sources to respiratory health on a population level.[5] To date particle sources have only been addressed in few epidemiological studies of respiratory health effects with non-conclusive results.[2 6 7] In panel studies, there were stronger associations between short term increases in Club Cell protein CC16 (a marker of increased lung permeability) concentration in urine and high levels of traffic PM than total PM.[8] In controlled experiments *in vitro,* exposing human lung cells to PM from different sources triggered very different pulmonary cell and DNA damage outcomes.[9] A deepened knowledge about effects of specific particle pollution sources is of particular interest to prioritize public health measures to reduce health effects of ambient air pollution.

In epidemiological studies, air pollution is most often assigned to certain sources by building exposure profiles from particle size distributions and relative concentrations of specific chemicals in the particles. Traffic pollution is for example characterized by NOx and ultrafine particles.[7] Particles from petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and lanthanum,[10] and particles from other industry is characterized by high levels of trace metals vanadium and nickel,[10 11] but are of course sector-dependent. Similarly, PM from marine traffic is subject to large uncertainties as fuel types and fleet types vary across the world.[12] However, this field of research is expanding rapidly as exposure science evolves with more sophisticated source specific models.[13] Beyond the importance of exposure composition and source, individual susceptibility to air pollution is modified by many factors, including genetic differences. Susceptibility related to genetic variability may improve our understanding of the physiological mechanisms underlying health effects of air pollution.[14 15] Glutathione S-transferase (GST) are involved in metabolizing reactive oxygen species to reduce oxidative stress.[16] GSTP1 SNPs have been reported to modify the risk of cardiovascular disease associated with exposure to NO_2[17] and to modify the association between NO_2 and lung function

decline in adults,[18] but findings are inconsistent and no meta-analysis has been performed.[19,20] Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has important functions in the innate immune system of the lungs, especially for opsonizing inhaled material.[21] SP-A gene polymorphisms are associated with development of serious pulmonary disease and are involved in the pulmonary defence against pathogens.[22] SNPs in SP-A coding regions have been associated with multiple respiratory diseases,[14] [23] as well as gene-environment interactions for smoking and chronic obstructive pulmonary disease.[24]

Many questions remain as to what components of air pollution are harmful in a general population, in particular at relatively low pollution exposures, and if such associations are modified by genetic factors. Thus, the aim of the current study was to investigate the effects of different PM sources determined from a state-of the arts dispersion model on lung function in a general population cohort, and to investigate lung function effects of genotype and gene-environment interaction with particle exposures types.

METHODS

Study population

The study population originates from the ADONIX (ADult-Onset asthma and NItric oXide) cohort, a random sample of subjects aged 24-76 years who were invited to participate in a clinical examination between 2001-2008, as previously described.[17 25-28] In brief, the overall participation rate was 46%, all participants provided data on residential address, lifestyle factors and education, presence of allergic airway inflammation and respiratory health, as well as clinical measurements of lung function, such as spirometry (single manoeuver) and nitric oxide in exhaled air (FENO). Blood samples were collected for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1 genes.

Exposure assessment

As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using dispersion modelling described in detail by Segersson and colleagues, 2017, including a detailed map of the area.[29] PM_{10} and $PM_{2.5}$ represent particles smaller than 10 and 2.5 micrometers (µm) respectively, whereas black carbon particles, PM_{BC}, are soot particles from combustion, notably vehicle exhaust. The specific sources that were investigated were traffic (exhaust and road wear for PM_{10} and $PM_{2.5}$, exhaust only for PM_{BC}), residential heating (predominantly house heating using wood assessed as area sources), marine traffic (averaged description from a bottom-up calculation using actual positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in Gothenburg dominated by refineries, energy plants, and other industry).[30] Background concentration (long-range transport particles), was also provided, but was estimated indirectly as the difference between total modelled local contribution and monitoring data from a central urban background station. Consequently, it showed no spatial variation and was not used for analyses. To refine the estimated contribution of traffic, an increment due to reduced ventilation in street canyons was added for the busiest streets. The increment was estimated as the difference between simulations with and without buildings using the OSPM model.[31] For each study participant's residential address at the date of clinical examination, annual mean values of pollutants were calculated separately for the five source categories and modelled exposure grid values of all PM fractions were matched to the year of the participant's clinical examination.

Outcome definitions

Dynamic spirometry including FEV_1 and FVC was performed with the subject in a sitting position using a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.[32] A local reference material was used for calculation of percent predicted (% predicted) of FEV_1 and FVC and

lower limit of normal, (LLN, the lower 5th percentile in healthy individuals) for FEV_1 and FVC.[33 34] Asthma was defined as reporting having had at least one asthma attack in the previous 12 months, and atopy was defined as having a positive phadiatop test. We used FEV_1, FVC and FEV_1/FVC below LLN as an indicator of clinically significant lung function reductions or air flow limitation.

Based on questionnaire replies, smoking status was categorised into current, former (no smoking during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles within residential regions, postcodes were categorised into four residential areas: Inner city, non-central city, suburban, and outer suburb or rural. Education was categorised in six categories: elementary school, lower secondary school, training or girls' school, grammar school, university, and "other" or not reported. Individuals who did not have information on all variables of interest were excluded, except for genotype, where analyses were run separately for each SNP. For this study we used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common) allele.

Statistical methods

First, descriptive statistics were calculated for the cohort and exposure data, and correlations between the total and source-specific exposure estimates for all PM size fractions were determined.

We estimated the association between each PM size fraction for each PM source, with predicted FEV_1 and FVC, in linear models. First, percent predicted lung function effects associated with PM size fractions and sources were analysed with exposure as a continuous variable, and estimated for an interquartile increase in exposure (additionally, the analysis was repeated for lung function in Litres). Second, we investigated the effects of the highest exposure values by setting high exposure cut-off for PM above the 90th percentile of population exposure, medium exposure at 50-90th percentile, with exposure at or below 50th percentile as the reference, and tested these for linear trends. To investigate clinically significant effects, we modelled increased risk of low lung function with LLN as a cut-off in

logistic models. To assess confounding, covariates were added to regression models one at a time and were retained in the model if the coefficient of PM was altered by more than 10% by their inclusion. The covariates included in the final models were age, sex, weight, education, residential area, smoking status, and exposure to passive smoking in the last 12 months.

For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes and lung function for all available SNPs in single-SNP linear models coded as minor allele dominant effects. We present nominal p-values for these exploratory analyses. To evaluate effect modification, we tested for interaction of the effects of exposure to different PM size fractions and sources on lung function by genotype, and report the adjusted means of a fitted model adjusted for all covariate variables. The significance of the interaction terms was evaluated using a likelihood ratio tests comparing the model with interaction term to the model without this term.

In sensitivity analysis, the effects of PM were analysed in models stratified by sex, smoking status, asthma status, atopic status, BMI categories, and age categories to evaluate possible confounding from any of these characteristics.

All regression results for change in lung function were reported as increment or decrement in % predicted. Change in mL is reported in the supplement. Odds ratios were obtained from the logistic model analyses. All results are presented as point estimates with 95% confidence intervals, and with p-values as appropriate. Analyses were performed in R studio.[35]

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting of the present research.

RESULTS

The ADONIX cohort includes 6685 individuals. After excluding individuals with missing data on explanatory variables such as smoking status (25), environmental tobacco smoke (76), and who had

missing, or very low quality of lung function (532), there were 6006 individuals, further 333 had a missing postcode, 315 did not have a European background, and 457 were outside the catchment area leaving 5216 for the main analysis. In the genetic analysis, up to 276 individuals had missing data. Finally, 5216 were included with information on the variables related to exposure and health outcomes used in this study and self-reported European ancestry. The mean age of the study population was 51.6 ±11.4 years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and 10.2% were exposed to passive smoking. A total of 12.6% (n=656) of the study population had FEV_1 below lower limit of normal and 9.5% (n=494) had FVC below LLN. The most common highest education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).

TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
Females	2789 (53.5%)
Respiratory health	
FEV_1 (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV_1, n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV_1/FVC, n (%)	548 (10.5%)
Smoking	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)

Passive smoking (last 12 months)	534 (10.2%)
Education	
Elementary school, n (%)	639 (12.2%)
Lower secondary School, n (%)	175 (3.3%)
Training/girls school, n (%)	389 (7.5%)
Grammar school, n (%)	1205 (23.1%)
University, n (%)	1954 (37.5%)
Other or not reported, n (%)	853 (16.4%)
Residential area	
Inner city, n (%)	945 (18.1%)
Non-central urban, n (%)	922 (17.7)
Suburban, n (%)	2178 (41.7%)
Outer suburb or rural, n (%)	1171 (22.4%)
Self-reported respiratory health**	
Current asthma, n (%)	462/4698 (9.0%)
MD diagnosed asthma, n (%)	348/4828 (6.9%)
Allergy***, n (%)	1220/3887 (23.9%)
BMI, mean (standard deviation)	26.1 (4.1)

FEV_1, forced expiratory volume in 1 second. FVC, forced vital capacity. LLN, lower limit of normal, the fifth percentile of a healthy population.*Lung function predicted from age, height and sex.[33]

**Adapted from questionnaire: "Have you had an asthma attack in the last 12 months?"

***Allergy was determined by a positive phadiatop test (IgE >0.35 IU/mL)

The mean annual air pollution levels at the residential addresses in the study population at study entry were moderate, at 15.7 μg/m^3 PM_{10}, 9.3 μg/m^3 $PM_{2.5}$, and 0.76 μg/m^3 PM_{BC} (Table 2). Background long-range transported particle matter constituted the larger proportion of exposure, contributing t75% and 76% of the total PM_{10} and $PM_{2.5}$ levels, respectively. The local emission source that contributed mostly to total PM_{10} was traffic, whereas residential heating contributed most to $PM_{2.5}$ (Table 2).

TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION

PM species and sources	Mean (SD)	50th percentile	90th percentile	IQR
PM_{10} total	15.7 (2.49)	15.47	18.80	3.05
Traffic (μg/m^3)	2.32 (1.75)	1.78	4.41	1.64
Residential heating (μg/m^3)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m^3)	0.03 (0.05)	0.02	0.08	0.03
Industry (μg/m^3)	0.11 (0.09)	0.09	0.23	0.10
$PM_{2.5}$ total (μg/m^3)	9.33 (1.75)	9.36	11.80	2.47
Traffic (μg/m^3)	0.74 (0.56)	0.57	1.41	0.52
Residential heating (μg/m^3)	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (μg/m^3)	0.03 (0.05)	0.05	0.08	0.03
Industry (μg/m^3)	0.07 (0.05)	0.06	0.12	0.06
PM_{BC} total (μg/m^3)	0.76 (0.32)	0.71	1.13	0.33
Traffic (μg/m^3)	0.36 (0.29)	0.27	0.69	0.25
Residential heating(μg/m^3)	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (μg/m^3)	0.01 (0.01)	0.00	0.02	0.01
Industry (μg/m^3)	0.01 (0.01)	0.01	0.01	0.01

IQR, interquartile range. SD, standard deviation.

Traffic was the largest contributor to PM_{BC}, and for PM_{BC} the contribution from long-range sources was considerably lower than for PM_{10} and $PM_{2.5}$, at 26%. Traffic sources were originally divided into exhaust and road wear, but as these were highly correlated (r>0.98) we combined the two into a single variable for traffic exposure and used that in the analyses. The correlation between total and traffic-related exposure was very high for PM_{BC} (r=0.99), whereas it was high for PM_{10} (r=0.75) and moderate for $PM_{2.5}$ (r=.040) (Table S1).

Effects of PM exposure

Percent predicted lung function were negatively associated with PM_{10} and $PM_{2.5}$ from traffic, and with PM_{BC} in linear models with continuous exposure. The effect estimates for particles from residential heating, marine traffic or industry indicated no strong or consistent adverse effects in the linear models (Table 3).

TABLE 3 ESTIMATED CHANGE IN FEV_1 AND FVC PER IQR CHANGE IN PM FROM DIFFERENT SOURCES

	Delta % predicted FEV_1				Delta % predicted FVC			
	B	95% CI			*B*	95% CI		
		Lower	Upper	p-value		Lower	Upper	p-value
PM_{10} Total	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	**-0.48**	**-0.89**	**-0.07**	**0.02**	**-0.46**	**-0.83**	**-0.08**	**0.02**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.24	0.24	1.00	-0.05	-0.27	0.17	0.66
Industry	-0.33	-0.78	0.11	0.14	-0.40	-0.80	0.01	0.05

$PM_{2.5}$ Total	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	**-0.47**	**-0.88**	**-0.07**	**0.02**	**-0.47**	**-0.83**	**-0.10**	**0.01**
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
PM_{BC} Total	**-0.56**	**-1.01**	**-0.12**	**0.01**	**-0.53**	**-0.94**	**-0.13**	**0.01**
Traffic	**-0.41**	**-0.78**	**-0.03**	**0.03**	**-0.43**	**-0.77**	**-0.09**	**0.01**
Residential heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
Industry	-0.40	-0.92	0.12	0.13	-0.38	-0.85	0.09	0.11

Parameter coefficients from in separate, single-pollutant models adjusted for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

IQR, interquartile range.

In models with categorical exposure (low, medium, and high exposure), there was a consistent trend across categories for traffic-related exposure in all particulate measures for both percent predicted FVC and FEV_1 (*p* for trend<0.05; for FEV_1 and PM_{BC} traffic p=0.09); the trend was slightly less strong and consistent for total PM exposure (Figure 1). There were no significant negative associations between percent predicted lung function and exposure to particles of any size from residential heating, marine traffic or industrial sources (Figure 1), nor were there statistically significant trends (Table S2). Estimating effects on lung function in mL rather than % predicted we observed significant decreases

of FEV_1 and FVC associated with PM_{10} traffic, $PM_{2.5}$ total and traffic as in the percent predicted analysis (Table S3 and Table 3). However, in this analysis PM_{10} and PM_{BC} from industry were also associated with decreased FEV_1 and FVC (Table S3). In a logistic regression, high exposure to any particle fraction from traffic were associated with increased odds ratio of having clinically significant reductions in FEV_1 and FVC (below LLN) ($p<0.05$; except $p=0.08$ for FEV_1 and PM_{BC}) (Table S4). The ratio FEV_1/FVC below LLN was not associated with any exposure (data not shown).

Genetic main effects

All SNPs were in Hardy-Weinberg equilibrium except rs1136450, which has one very rare genotype (n=12). The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%. (Table S5). In a main effect analysis without considering environmental exposure, minor allele carrier status of three GST SNPs was associated with lung function outcomes in minor allele dominant genetic models. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV_1 reductions by -0.80% (p=0.044) and -0.90% (p=0.017), respectively, and FVC reductions were seen in minor allele carriers of the same GSTP1 SNP rs762803 (-0.74%, p=0.042) and the GSTT1 null genotype assessed with SNP rs2266637 (-1.434%, p=0.001). No main effect associations were found with SP-A SNPs (Table S5).

Effect modification of PM effects

$PM_{2.5}$, which had marginally more consistent effects for traffic-related exposure, was used for exploratory interaction analyses. The effect of genotype and exposure to $PM_{2.5}$ from all sources was analysed in interaction models, and SNPs with exposure-interaction p-values below 0.1 are shown in Table S6. The number of significant interactions was higher than expected by chance. The most plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV_1 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result should, however, be seen as highly exploratory. Analysing the data stratifying by smoking status, atopy, asthma status, and BMI category showed no significant effect modification on the estimated effect of

PM2.5 from traffic sources on lung function in either linear or logistic analysis. Although the estimated effect of exposure differed between the subgroups, all confidence intervals overlapped (Table S7).

DISCUSSION

In a general population cohort we observed significant associations between lung function and modelled exposure to PM_{10} and $PM_{2.5}$ from traffic as well as PM_{BC}. The association between FEV_1 and FVC was consistently present in 1) linear models with continuous exposure (Table 3) , and 2) in models in which exposure was expressed as categories, high exposure (above the 90th percentile) compared to low exposure (<50th percentile) with significant trends across three exposure strata (Figure 1, Table S2). In the analyses, the observed average decreases were numerically small and without individual-level clinical significance, but in logistic regression models with binary outcomes, FEV_1 below LLN was associated with high exposure to PM_{10} and $PM_{2.5}$ traffic particles, and FVC below LLN was associated with traffic particles in all size fractions as well as total PM_{BC} (Table S4). This pattern was also found when exposure was expressed categorically for a continuous outcome (Figure 1). We observed no associations with airflow limitation, rather the negative associations with exposure means that such effects, which could possibly explained by the parallel reduction of both FEV_1 and FVC.

Because we observed significant associations between percent predicted lung function and most traffic-related exposure metrics on a population level, and no obvious associations were found between any fractions of PM from residential heating, marine traffic or industry, our results indicate that exposure to PM from traffic is particularly detrimental to lung function. However, we cannot rule out that we observed the lack of associations to other sources were due to a lower accuracy in exposure assessment for these sources. Furthermore, the relative contribution of marine traffic, industry and residential heating to total PM was modest (Table 2), which could also lead to inaccurate or low estimates without statistical significance. There are hypotheses postulating that exposure to newly formed particles, such as from traffic close to the domestic address, may be more potent and reactive, but so far there seem to be no consensus.[29 36] Interestingly, in the analysis of crude lung function (in mL, rather than percent of predicted) we also observed associations with particles of

industrial origin, suggesting that they could be modified by factors related to age, height and sex which are accounted for in the percent predicted value.

In spite of there being moderate to high correlations (0.75, 0.42 and 0.99) between total PM and traffic related PM in any of the three fractions (Table S1), total PM_{10} and $PM_{2.5}$ were not significantly associated with reductions in percent predicted FVC and FEV_1. Residential heating is the second largest local contribution to total PM, and we observed negative correlations between PM from residential heating and total PM as well as PM from other sources. PM from residential heating could thus be interpreted as an indicator of low exposure to other sources of air pollution which might contribute to explaining the few suggested inverse (positive) associations seen in some categorical analyses between PM from residential heating and FEV_1 and FVC (e.g. Figure 1).

For GSTP and GSTT genotypes, where carrying the minor or null allele, were associated with decreased percent predicted FEV_1 and FVC, whereas no direct effects of SP-ASNPS were found (Table S4). Gene-environment interactions were tested for all SNPs and all PM sources and size fraction, but significant and biologically plausible interactions were only observed between specific SP-A SNPs and exposure to $PM_{2.5}$ from marine traffic and industrial sources, and not for traffic or total PM, where most direct effects where observed. We thus infer that it is possible that detrimental effects from marine traffic and industry PM t may affect specific individuals with genetic susceptibilities.[14] Industrial exposure in Gothenburg is concentrated along the northern mouth of the Göta Älv River and is dominated by a power plant and oil refineries. PM from marine traffic is also concentrated along the river.

During initial analysis and covariate selection, we found that residential region was an effect modifier, and included this as a covariate in the study. Other studies of lung function within a single region have adjusted for municipality to avoid confounding of the results which is likely due socio-economic distribution of the study population in some urban areas, where high-exposed areas also have a high proportion of individuals with high socio-economic status which entails other risk factor panorama and health behaviours.[37]

In a previous study on the same cohort population, short distance to the nearest road was found to be associated with decreases in FEV_1 and FVC.[38] Comparing with other studies, the size of the estimated change in lung function in our study are similar and within confidence intervals of those reported from the UK biobank.[3] The pollution levels found in the current study were moderate compared to those presented in the study from Adam and colleagues, reporting significant associations for both FEV_1 and FVC in adults related to long term exposure to NO_2, NOx and PM_{10}, but not $PM_{2.5}$ or coarse PM in a meta-analysis of the ESCAPE data.[7] In our study, both of NOx and NO_2 were highly correlated with traffic PM_{10}, $PM_{2.5}$ and PM_{BC} (all correlations r>0.79), for the years that both NOx and NO_2 and source specific PM estimates were available.

Effects specifically of exposure to industrial emissions have not been widely studied, and industry emissions are often pooled with other sources,[29] or considered negligible as high stacks disperse the emissions.[39] Studies of respiratory health with source specific results generally find associations mainly with traffic: In the study of Jacquemin and colleagues,[8] only traffic, and not industry-specific particles were associated with the lung damage marker CC16. Krall and colleagues[13] observed only effects from tailpipe exhaust on lung function and eNO. Billet and colleagues[9] exposed cells *in-vitro* to particles from a highly industrialized environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response. Peng and colleagues[6] observed that PM from vehicle emissions, diesel engines and wood burning were associated with the largest increases in emergency hospital admissions for CVD and respiratory disease.[6] In a multi-city European study[40] there were negative associations between FEV_1 and PM from nickel and sulphur, however results were not consistent between cities, perhaps reflecting the heterogeneity in particle compositions in different cities in the study.[41]

SP-A has the ability to bind and help clear pathogens but also particle matter from the lungs by opsonisation[22] and is activated in response to exposure to Ozone, another major air pollutant[42] Previous literature suggest that SNPs of SP-A are associated with defect opsonisation, and hence

increased risk for viral infections,[43] but likely also for adverse effects of particle exposure (as well as volatile exposures.[22] We found a significant interaction between polymorphisms of two SP-A1 SNPs and the association between exposure to PM from industrial sources and lung function. Other studies have found rs1059057 to be associated with acute lung injury[22] and cystic fibrosis,[44] and rs1136451 with susceptibility to COPD and analysed gene-environment effects from tobacco smoking.[24] The SP-A 2 SNP rs4253527 has been associated with tuberculosis.[22]

We observed no gene-environment interactions with any GSTT or GSTP SNPS. The GSTP SNP rs1695 has been associated with possible increased asthma risk of air pollution exposure,[19] whereas we found a main effect with lower FEV_1 in the current study of adults, but no interactions. These genetic interactions results should be seen as exploratory and be interpreted with caution.

Strengths and limitations

The cohort data used in this study were collected to study respiratory health, and provides a rich dataset containing a large number of variables of interest. In the model selection, adding additional covariates as potential confounders did not affect the regression estimates substantially. Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered 2001–2003) and showed that women, the elderly, and individuals with university education were more likely to participate.[28] As we adjusted for these covariates and as exposure was unknown to participants, this is not likely to bias the current results.

The number of individuals who fell below the lower limit of normal for both FEV_1 and FVC was rather high, as this value is defined as the 5th percentile in a healthy, non-smoking population. It is possible that individuals with respiratory issues, as well as past and present smokers, are more likely to take part in a study such as ADONIX.[28] On the other hand, with clinical outcome measures and an exposure which was not known to the participants, this is an unlikely source of important bias.

In this study, complete residential histories, including duration of residence, were not available. Instead, we used a single modelled value for residential exposure that was matched by year of

participation for each individual, rather than a complete longitudinal exposure history over multiple years. We consider this a reasonable approach, as the between-year correlation in air pollution concentrations and emissions in a certain location is very high.

As people spend a fair proportion of their time outside their home, and our results are based on modelled air pollution data at the place of residence, the exposure represents an approximation of the real exposure. However, this is an established method which provides a fair picture of the actual exposure. The resulting, and likely nondifferential, misclassification of exposure would, however, then to shrink risk estimates towards the null. The model was developed using new emissions inventories, updated information on vehicle composition, and had been further verified by measurements.[29] However, for residential heating, the source assignment is based on proxies such as building type, as no actual source inventory was available, and may have a poorer performance.

The very high correlations between traffic-related PM_{10}, $PM_{2.5}$ and PM_{BC} (Table S1) mean that it is difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to high correlations between the various PM source measures also meant we had to refrain from using multi-pollutant models, meaning that f estimates associated with each exposure type must be interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent associations with FEV_1 and FVC, whereas the other source-specific exposures did not.

CONCLUSION

In this large study of clinically measured outcomes in a general population sample we found that exposure to traffic particles of all three studied PM species and size fractions were associated with reductions in FEV_1 and FVC and increased risk of low FEV_1 and FVC (below LLN), supporting the need for measures to reduce urban pollution from traffic to protect urban populations. Furthermore, we found intriguing suggestions in our exploratory analysis that the SP-A1 gene may play a part in susceptibility to air pollution from industrial sources, possibly due to its very different composition.

Author Contributions

HKC analysed the data and drafted the manuscript. FN, KT, and A-CO provided the cohort and genetic data, contributed to essential parts of the introduction and discussion and the final manuscript. DS provided and documented the PM exposure data. All authors approved the final version of the manuscript and contributed to the discussion.

Data statement

Additional data from the ADONIX study exist and are held by the authors.

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Competing interests

None declared.

Ethics approval: The Västra Götaland Region ethical review board approved of the study (ref no. Ö 092-01) and participants gave informed consent.

Legends

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50_{th} to 90_{th}) and high (above 90_{th} percentile) concentration of source-specific PM

Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV_1 and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

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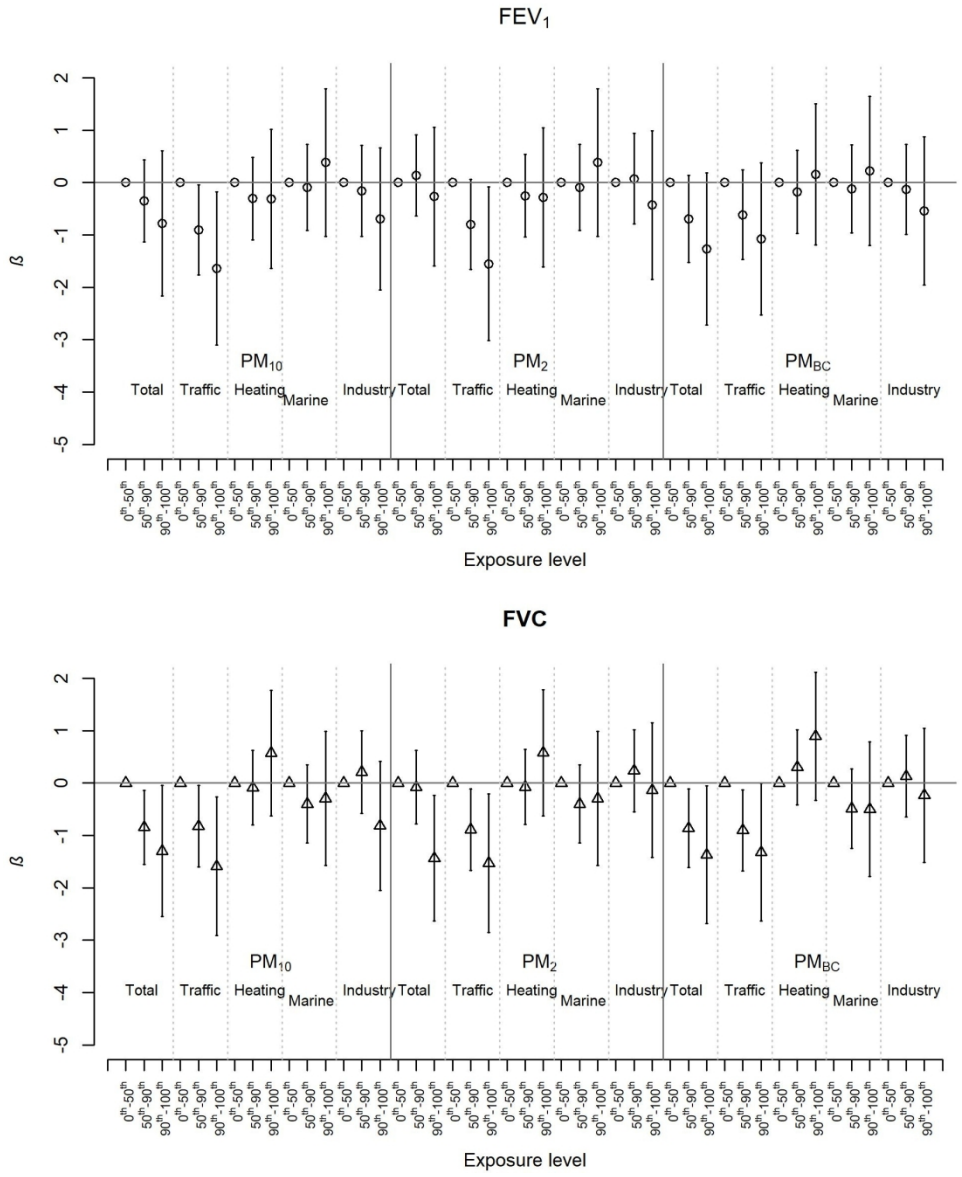

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

169x203mm (300 x 300 DPI)

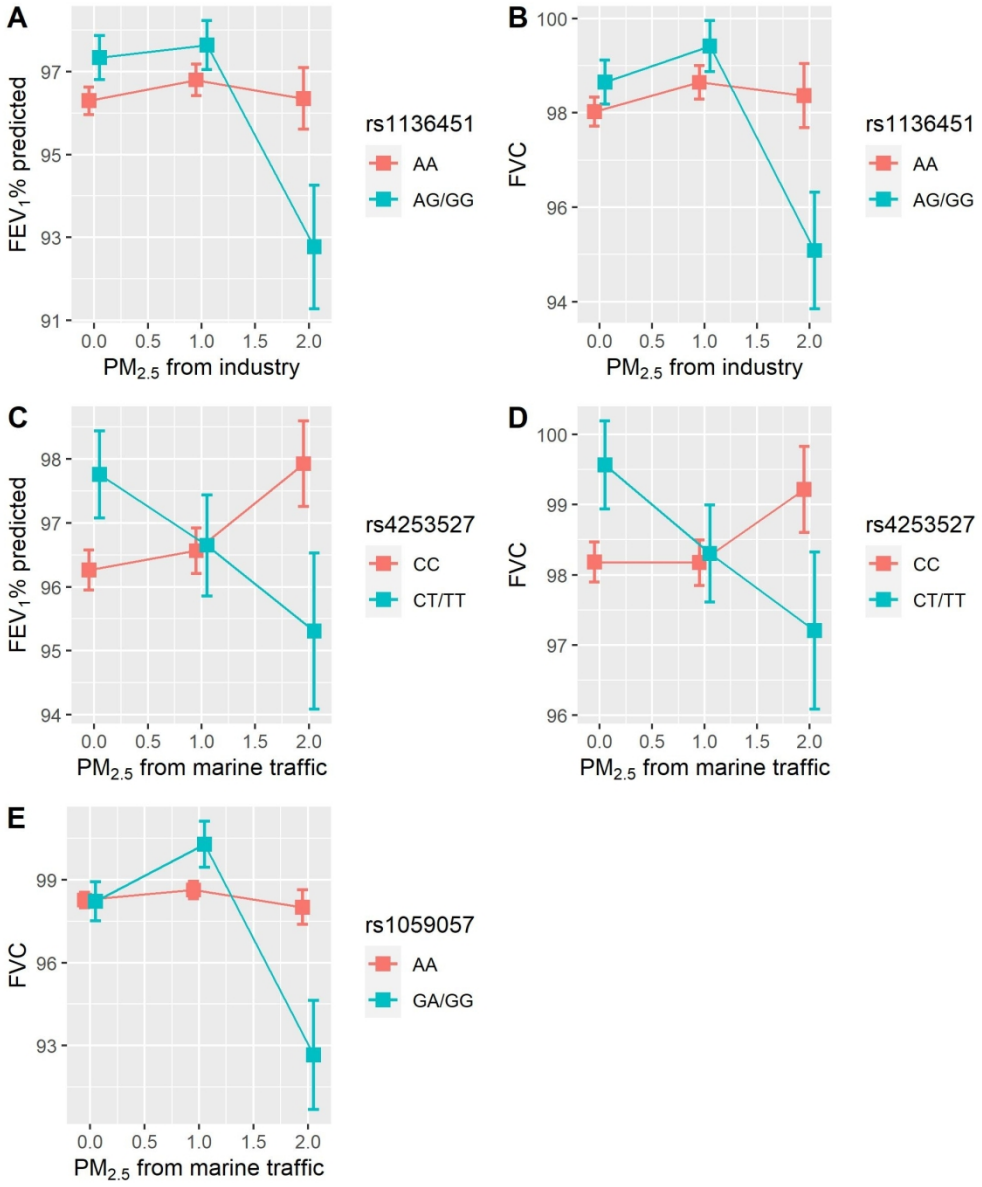

Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV_1 and FVC in exposure categories to select PM sources with standard error bars. Dotted lines represent effects on minor allele carriers

169x203mm (300 x 300 DPI)

Table S1 Correlation (Pearson's) matrix of exposure

		PM_{10}					$PM_{2.5}$					PM_{BC}				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM_{10}	Total	1														
	Traffic	0.75*	1													
	Residential heating	-0.43	-0.70*	1												
	Marine traffic	0.06	0.44	-0.83*	1											
	Industry	-0.32	0.30	-0.60*	0.63*	1										
$PM_{2.5}$	Total	0.89*	0.37	-0.12	-0.22	-0.66*	1									
	Traffic	0.77*	1*	-0.70*	0.43	0.27	0.40	1								
	Residential heating	-0.43	-0.70*	1*	-0.83*	-0.60*	-0.12	-0.70*	1							
	Marine traffic	0.06	0.44	-0.83*	1*	0.63*	-0.22	0.43	-0.83*	1						
	Industry	-0.23	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1					
PM_{BC}	Total	0.83*	0.98*	-0.59*	0.32*	0.13	0.49	0.99*	-0.59*	0.32	0.13	1				
	Traffic	0.83*	0.99*	-0.69*	0.40*	0.19	0.48	1*	-0.69*	0.40	0.21	0.99*	1			
	Residential heating	-0.41	-0.69*	1*	-0.83*	-0.62*	-0.09	-0.69*	1*	-0.83*	-0.73*	-0.58*	-0.68*	1		
	Marine traffic	0.08	0.45	-0.83*	1*	0.62*	-0.20	0.44	-0.83*	1*	0.71*	0.33	0.41	-0.83*	1	
	Industry	-0.24	0.29	-0.70*	0.72*	0.94*	-0.54*	0.27	-0.70*	0.72*	1*	0.13	0.21	-0.72*	0.70*	1

* $p<0.05$

Table S2 Trends in change in FEV_1 and FVC (% predicted) across exposure strata from low (0-50th percentile) to high (above 90th percentile) concentrations of source-specific PM (Figure 1)

	FEV_1				FVC			
	β	95% CI		*p*	*β*	95% CI		*p*
		Lower	Upper			Lower	Upper	
PM_{10}								
Total	-0.37	-0,97	0,22	0.22	**-0.73**	-1,27	-0,19	**0.01**
Traffic	**-0.85**	-1,51	-0,19	**0.01**	**-0.81**	-1,40	-0,21	**0.01**
Residential heating	-0.21	-0,79	0,37	0.47	0.15	-0,38	0,67	0.59
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.29	-0,91	0,33	0.36	-0.22	-0,79	0,35	0.45
$PM_{2.5}$								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	**-0.79**	-1,45	-0,13	**0.02**	**-0.81**	-1,41	-0,21	0.01
Residential heating	-0.18	-0,77	0,40	0.53	0.15	-0,37	0,68	0.57
Marine traffic	0.08	-0,54	0,71	0.32	-0.24	-0,81	0,32	0.29
Industry	-0.12	-0,76	0,53	0.72	0.03	-0,55	0,62	0.91
PM_{BC}								
Total	**-0.66**	-1,30	-0,01	**0.05**	-0.75	-1,34	-0,17	0.01
Traffic	-0.57	-1,22	0,09	0.09	-0.75	-1,34	-0,16	0.01
Residential heating	-0.02	-0,61	0,58	0.95	0.39	-0,15	0,93	0.16
Marine traffic	0.03	-0,61	0,67	0.33	-0.34	-0,91	0,24	0.30
Industry	-0.22	-0,86	0,42	0.49	-0.03	-0,61	0,55	0.92

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

Table S3 Change in FEV_1 and FVC (mL) per IQR change in PM exposure

		FEV1			FVC		
			95% CI			95% CI	
	IQR (µg/m³)	*β*	*Lower*	*Upper*	*β*	*Lower*	*Upper*
PM_{10}							
Total	3.05	-23	-46	0	-11	-30	8
Traffic	1.64	**-23**	**-43**	**-4**	**-20**	**-36**	**-4**
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-8	16	4	-6	13
Industry	0.10	**-26**	**-47**	**-5**	**-18**	**-35**	**-1**
$PM_{2.5}$							
Total	2.47	**-28**	**-54**	**-3**	-5	-26	15
Traffic	0.52	**-24**	**-43**	**-5**	**-20**	**-36**	**-4**
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-38	46	4	-30	38
Industry	0.06	**-24**	**-49**	**0**	**-18**	**-38**	**2**
PM_{BC}							
Total	0.33	**-29**	**-50**	**-8**	**-25**	**-42**	**-7**
Traffic	0.25	**-24**	**-42**	**-6**	**-18**	**-33**	**-4**
Residential heating	0.07	4	-21	28	-11	-31	8
Marine traffic	0.01	3	-8	15	3	-6	13
Industry	0.01	**-27**	**-51**	**-2**	**-20**	**-40**	**0**

Change estimated from linear regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months

Table S4 Odds ratio of having FEV_1 and FVC below LLN in medium and high exposure strata by PM source and size fraction*

		LLN FEV_1				LLN FVC			
			95% CI				95% CI		
Model	**Percentile**	OR	**lower**	upper	p	OR	**lower**	upper	p
PM_{10}									
Total	0-50th	-	-	-	-				
	50th-90th	1.05	0.87	1.26	0.61	**1.23**	**1.00**	**1.51**	**0.05**
	90th-100th	1.18	0.86	1.62	0.31	**1.40**	**0.98**	**1.99**	**0.06**
Traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18
	90th-100th	**1.46**	**1.06**	**2.02**	**0.02**	**1.45**	**1.00**	**2.08**	**0.05**
Residential heating	0-50th	ref	-	-			ref	-	-
	50th-90th	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79
	90th-100th	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49
$PM_{2.5}$									
Total	0-50th								
	50th-90th	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77
	90th-100th	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11
Traffic	0-50th	ref	-	-	-				
	50th-90th	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09
	90th-100th	**1.47**	**1.06**	**2.03**	**0.02**	**1.54**	**1.07**	**2.21**	**0.02**
Residential heating	0-50th	ref	-	-	-	ref	-	-	
	50th-90th	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87
	90th-100th	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90th-100th	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50th					ref	-	-	
	50th-90th	0.91	0.74	1.12	0.38	1.03	0.82	1.30	0.79

Supplementary tables for ADONIX: Lung function and source specific PM

	90th-100th	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
PM_{BC}									
Total	0-50th					ref	-	-	
	50th-90th	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
	90th-100th	1.34	0.97	1.86	0.08	**1.46**	**1.02**	**2.09**	**0.04**
Traffic	0-50th	ref	-	-	-				
	50th-90th	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
	90th-100th	1.37	0.98	1.90	0.06	**1.55**	**1.08**	**2.23**	**0.02**
Residential heating	0-50th	ref	-	-	-	ref	-	-	
	50th-90th	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
	90th-100th	0.80	0.57	1.11	0.18	**0.64**	**0.44**	**0.94**	**0.02**
Marine traffic	0-50th	ref	-	-		ref	-	-	
	50th-90th	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
	90th-100th	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
Industry	0-50th					ref	-	-	
	50th-90th	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
	90th-100th	0.99	0.72	1.35	0.95	1.09	0.77	1.56	0.62

ORs from regression models adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.FEV_1, forced expiratory volume in 1 second, FVC, forced vital capacity, LLN, lower limit of normal, the fifth percentile of a healthy population, according to formula from Brisman et al., 2017.

Table S5 Genetic main effects: Changes in FEV_1 and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs

		FEV_1				FVC			
	N (%)	*β*	95% CI Lower	Upper	p	β	95% CI Lower	Upper	*p*
GSTP									
rs1138272									
(TT+CT)	707 (14.3)								
***vs* CC**	4250 (85.7)	0.513	-0.539	1.565	0.339	0.790	-0.161	1.741	0.103
rs596603									
(TT+GT)	3363 (68.0)								
***vs* GG**	1581 (32.0)	-0.336	-1.126	0.455	0.405	-0.216	-0.931	0.499	0.554
rs762803									
(AA+AC)	3309 (67.0)								
***vs* CC**	1633 (33.0)	**-0.802**	**-1.583**	**-0.02**	**0.044**	**-0.736**	**-1.443**	**-0.028**	**0.042**
rs1695									
(AG+GG)	2683 (54.4)								
***vs* AA**	2244 (45.5)	**-0.902**	**-1.643**	**-0.16**	**0.017**	-0.575	-1.246	0.095	0.093
GSTT									
rs2266637									
GG	1005 (23.8)								
***vs* CC**	3219 (76.2)	-0.378	-1.331	0.575	0.437	**-1.431**	**-2.293**	**-0.57**	**0.001**
SP-A 1									
rs1136450									
(CC+GC)	2926 (63.8)								
***vs* GG**	1660 (36.2)	-0.106	-0.899	0.704	0.807	-0.106	-0.832	0.62	0.774
rs1136451									
(GG+GA)	1352 (29.7)								
***vs* AA**	3195 (70.3)	0.498	-0.348	1.345	0.248	0.257	-0.51	1.023	0.511
rs1059057									
(GG + GA)	579 (12.6)								
***vs* AA**	4018 (87.4)	0.155	-1.003	1.313	0.793	0.073	-0.977	1.124	0.891
rs4253527									

(TT+TC)	848 (18.5)								
***vs* CC**	3735 (81.5)	0.479	-0.513	1.471	0.344	0.508	-0.392	1.408	0.269
SP-A 2									
rs1059046									
(GG+GT)	2814 (61.8)								
***vs* TT**	1741 (38.2)	0.070	-0.724	0.865	0.862	0.038	-0.682	0.759	0.917
rs1965707									
(AA+AG)	2103 (46.2)								
***vs* GG**	2449 (53.8)	0.085	-0.686	0.856	0.829	0.255	-0.446	0.956	0.476
rs1965708)									
(TT+TG)	1551 (33.8)								
***vs* GG**	3041 (66.2)	-0.583	-1.397	0.231	0.160	-0.342	-1.08	0.396	0.364

With adjustment for age, weight, education, area of residence, smoking status, and exposure to environmental tobacco smoke in the last 12 months.

Table S6 Interaction between genotype (minor allele carriers) and total and source specific PM on lung function in a linear model

Gene	SNP	INTERACTION (p)* Total	Traffic	Residential heating	Marine traffic	Industry
FEV_1						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.05
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTT1	rs2266637	0. 01	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	**0.04**	**0.01**
SP-A1	rs1059057	0. 05	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	**0.02**	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	0.06	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	0.08	P>0.1
FVC						
GSTP1	rs1138272	P>0.1	P>0.1	P>0.1	P>0.1	0.06
GSTP1	rs596603	P>0.1	P>0.1	P>0.1	P>0.1	0.07
GSTP1	rs762803	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
GSTP1	rs1695	P>0.1	P>0.1	P>0.1	P>0.1	**0.03**
GSTT1	rs2266637	0.048	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	**rs1136450**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	rs1136451	P>0.1	P>0.1	P>0.1	P>0.1	0.03
SP-A1	rs1059057	P>0.1	0.07	0.08	P>0.1	**0.01**
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	**0.03**	P>0.1
SP-A2	**rs1059046**	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965707	P>0.1	P>0.1	P>0.1	P>0.1	P>0.1
SP-A2	rs1965708	P>0.1	P>0.1	P>0.1	**0.03**	P>0.1

Interaction models were adjusted for age, weight, education, area of residence, smoking status and exposure to environmental tobacco smoke in the last 12 months.

Table S7 Sensitivity analysis - ESTIMATED CHANGE IN FEV_1 AND FVC PER IQR CHANGE IN $PM_{2.5}$ FROM traffic in various subgroups of the cohort

Linear regression	FEV_1				FVC			
		95% CI				95% CI		
	β	Lower	Upper	*p*	β	Lower	Upper	*p*
Smoking status								
Never smoker	-0.26	-0.84	0.33	0.10	-0.47	-1.01	0.07	0.09
Former smoker	-0.10	-0.83	0.61	0.50	-0.33	-0.98	0.31	0.31
Current smoker	-1.61	-2.50	-0.72	0.06	-0.71	-1.52	0.10	0.09
Atopic sensibilisation*								
No atopy	-0.84	0.13	0.08	<0.00	-0.36	-0.80	0.08	0.03
Atopy	-1.46	0.12	0.05	<0.00	-0.67	-1.37	0.04	0.37
Asthma*								
No asthma	-0.38	-0.79	0.04	0.07	-0.44	-0.82	-0.06	0.02
Asthma	-0.70	-2.33	0.92	0.40	-0.58	-1.89	0.74	0.39
Body mass index (BMI. kg/m2)								
Underweight (BMI <= 20)	0.41	-2.06	2.88	0.74	0.22	-2.11	2.55	0.85
Normal weight (BMI 0-25)	-0.08	-0.70	0.53	0.79	-0.29	-0.83	0.26	0.30
Overweight (BMI >25)	-0.85	-1.42	-0.29	<0.00	-0.64	-1.15	-0.13	0.01

Logistic regression		95% CI				95% CI		
Smoking status	OR	Lower	Upper	*p*	OR	Lower	Upper	*p*
Never smoker	1.43	1.08	1.90	0.01	1.38	1.04	1.85	0.03
Former smoker	1.24	0.94	1.64	0.12	1.06	0.87	1.30	0.72
Current smoker	0.98	0.69	1.39	0.90	1.26	0.97	1.63	0.27
Atopic sensibilisation*								
No atopy	1.13	0.92	1.39	0.23	1.23	0.98	1.55	0.07
Atopy	1.38	0.98	1.95	0.06	1.26	0.98	1.62	0.26
Asthma**								
No asthma	1.21	0.99	1.47	0.05	1.27	1.03	1.57	0.03
Asthma	1.18	0.76	1.82	0.47	1.24	0.91	1.69	0.41
Body mass index (BMI. kg/m2)								

Supplementary tables for ADONIX: Lung function and source specific PM

Underweight (BMI <= 20)	1.15	0.39	3.32	0.81	1.02	0.44	2.34	0.96
Normal weight (BMI 0-25)	1.03	0.75	1.41	0.85	1.06	0.84	1.35	0.75
Overweight (BMI >25)	1.35	1.09	1.66	<0.00	1.36	1.19	1.56	0.01

FEV_1, forced expiratory volume in 1 second. FVC, forced vital capacity. IQR, interquartile range. β from linear regression models adjusted for age, weight, education, area of residence, and smoking status, excluding the stratification variable in the models stratified for smoking status and BMI. ORs from generalized linear regression models adjusted for age, weight, education, area of residence, and smoking status excluding the stratification variable in the models stratified for smoking status and BMI.

*Allergy was determined by a positive phadiatop test (IgE >0.35 IU/mL)

**Answering “yes” to “Have you had an asthma attack in the last 12 months?”

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Ok,
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction pages 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, last introduction paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	In the abstract, title, and aims (last paragraph of introduction)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods line 102,
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Line 102 and and references therein
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Does not apply
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	From line 133
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*From line 102 (cohort) and line 111 (exposure)*
Bias	9	Describe any efforts to address potential sources of bias	See statistical methods
Study size	10	Explain how the study size was arrived at	From line 103
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	From line 132
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	From line 154
		(*b*) Describe any methods used to examine subgroups and interactions	Line 171 and 173
		(*c*) Explain how missing data were addressed	Lines 281-286
		(*d*) If applicable, explain how loss to follow-up was addressed	Does not apply
		(*e*) Describe any sensitivity analyses	Line 173-175.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	Line 281-286.

		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8, exposure page 8-9.
		(b) Indicate number of participants with missing data for each variable of interest	Does not apply
		(c) Summarise follow-up time (eg, average and total amount)	Does not apply
Outcome data	15*	Report numbers of outcome events or summary measures over time	See table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Adjusted estimates are reported as main results, unadjusted estimates can be provided upon request. Interaction results are reported without adjustment.
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Does not apply
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Line 244-246.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Line 248 onwards.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See article summary, from line 50, and in discussion line 331 onward
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion and interpretation lines 253 and onwards. Results from similar studies lines 291-316.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 364 onward
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported on manuscript central and statements.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.