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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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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 ADult-Onset asthma and NItric oXide 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 men.

Primary and secondary outcome measures The primary outcome was forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Secondary outcome measures 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 (% predicted) FEV_1 by −0.48% (95% CI −0.89% to −0.07%) and −0.47% (95% CI −0.88% to −0.07%) per IQR 3.05 and 2.47 µg/m^3, respectively, and with decreases in % 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 % 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 $PM_{2.5}$.

Strength and limitations of this study

- An extensive dispersion model of source-specific particle matter 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 standardised manoeuvre 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 particle matter (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 prioritise 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, characterised by NO_x and ultrafine particles.[7] Particles from petrochemical industries are characterised by trace elements such as nickel, cobalt, caesium and lanthanum,[10] and particles from other industry are characterised 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 metabolising reactive oxygen species to reduce oxidative stress.[16] GSTP1 single-nucleotide polymorphisms (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 opsonising 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-art 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 ADult-Onset asthma and NItric oXide (ADONIX) Cohort, a random sample of subjects aged 24–76 years who were invited to participate in a clinical examination between 2001 and 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. 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, the Swedish Meteorological and Hydrological Institute modelled source-specific, annual PM concentrations for different size fractions for each calendar year in the period 1990–2011 using dispersion modelling described in detail by Segersson *et al*, including a detailed map of the area.[29] PM_{10} and $PM_{2.5}$ represent particles smaller than 10 and 2.5 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 Operational Street Pollution 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 forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), was performed with the subject in a sitting position using a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen pulmonary function testing, PFT (Vyaire, Mettawa, Illinois, USA) was used. All procedures were performed according to American Thoracic Society/European Respiratory Society (ATS/ERS)

standards.[32] A local reference material was used for calculation of percent-predicted (% predicted) 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. On 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, an 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, % 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 50th–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, and 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 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, body mass index (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. ORs were obtained from the logistic model analyses. All results are presented as point estimates with 95% CIs, 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 men, 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 LLN 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).

The mean annual air pollution levels at the residential addresses in the study population at study entry were moderate, at 15.7 $\mu g/m^3$ PM_{10}, 9.3 $\mu g/m^3$ $PM_{2.5}$, and 0.76 $\mu g/m^3$ PM_{BC} (table 2). Background long-range transported PM constituted the larger proportion of exposure, contributing 75% 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 1 Characteristics of the study population

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5)
Females, n (%)	2789 (53.5)
Respiratory health	
FEV_1 (% predicted*), mean (SD)	96.6 (13.7)
FVC (% 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)
Medical doctor-diagnosed asthma, n (%)	348/4828 (6.9)
Allergy‡, n (%)	1220/3887 (23.9)
Body mass index, mean (SD)	26.1 (4.1)

*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).
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal, the fifth percentile of a healthy population.

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=0.040) (online supplemental 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).

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 % 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 % 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 (online supplemental 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 % predicted analysis (online supplemental 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 (online supplemental table S3). In a logistic regression, high exposure to any particle fraction from traffic were associated with increased OR of having clinically significant reductions in FEV_1 and FVC (below LLN) (p<0.05; except p=0.06 for FEV_1 and PM_{BC}) (online supplemental 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% (online supplemental 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 (online supplemental table S5).

Effect modification of PM effects

$PM_{2.5}$, which had marginally more consistent effects for traffic-related exposure, was used for exploratory

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

PM, particle matter.

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 online supplemental 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

Table 3 Estimated change in FEV_1 and FVC per IQR change in PM from different sources

	Delta % predicted FEV_1				Delta % predicted FVC			
		95% CI				95% CI		
	B	Lower	Upper	P value	B	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.
Significant results are presented in bold font,

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PM, particle matter.

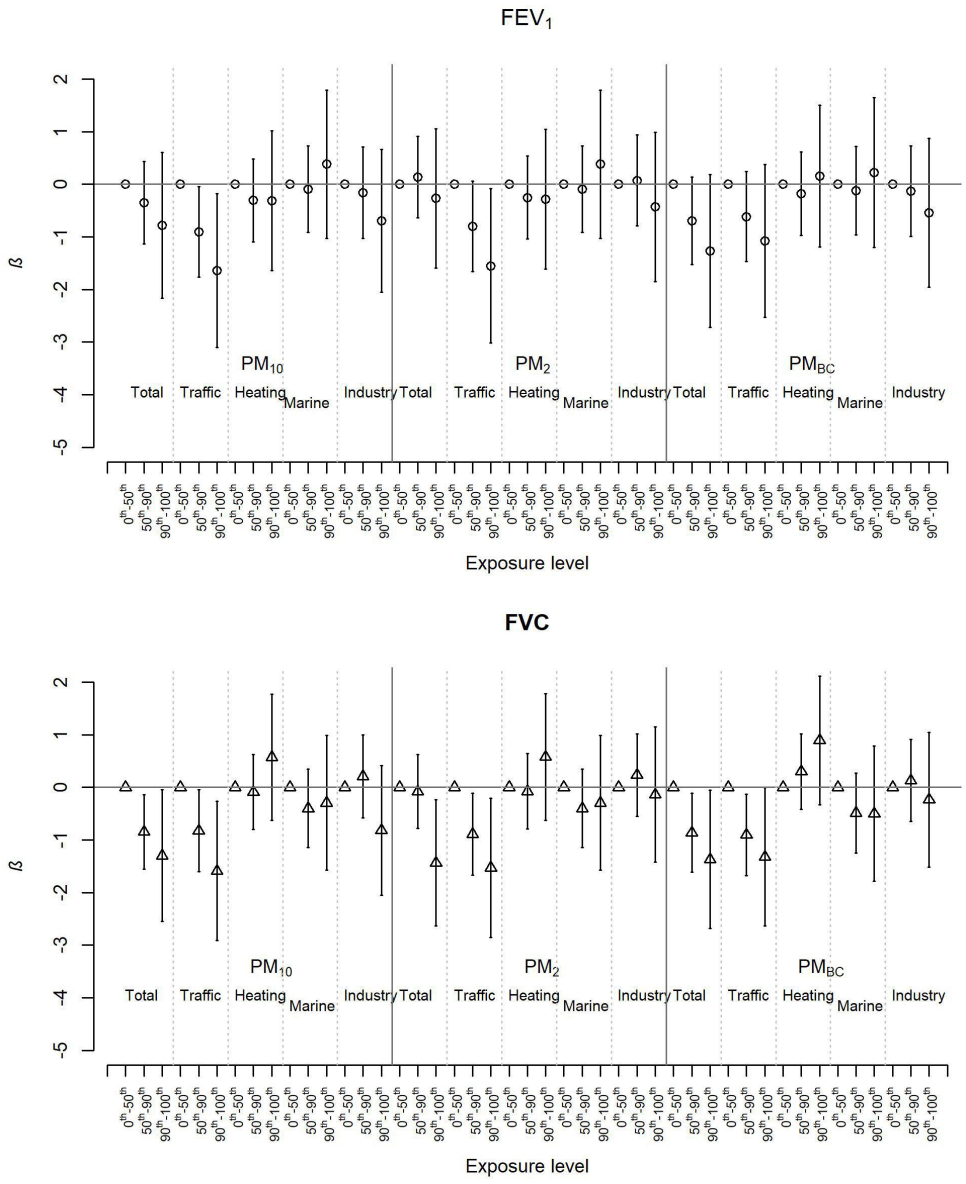

Figure 1 Change in FEV_1 and FVC (% predicted) associated with exposure to medium (50th–90th) and high (above 90th percentile) concentration of source-specific PM. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PM, particle matter.

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 $PM_{2.5}$ 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 (online supplemental 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 with low exposure (<50th percentile) with significant trends across three exposure strata (figure 1 and online supplemental 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} (online supplemental table S4). This pattern was also found when exposure was expressed categorically

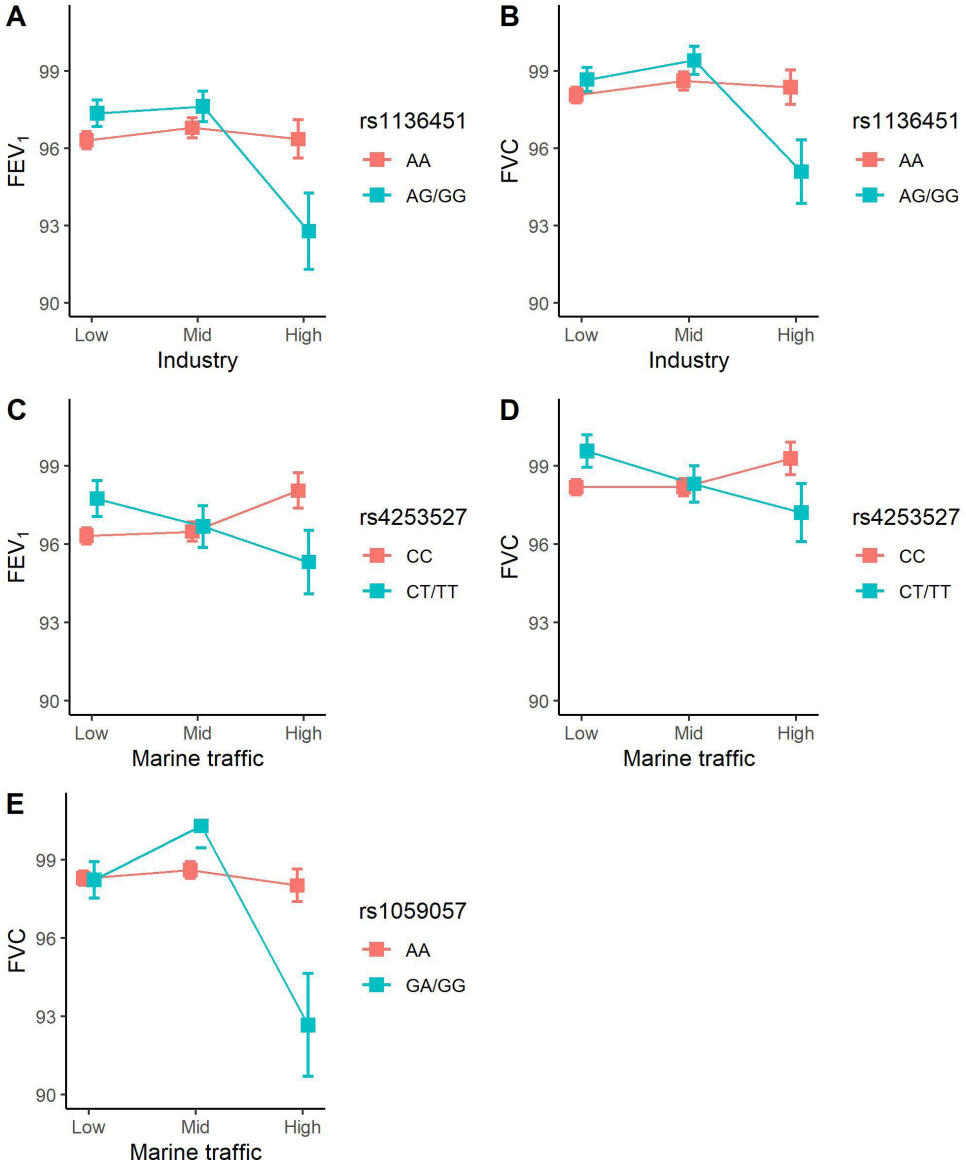

Figure 2 Unadjusted gene–environment interactions between selected single nucleotide polymorphisms and % predicted values of FEV_1 and FVC in exposure categories of selected PM2.5 sources. A) Interaction between PM2.5 from industry and rs1136451 on %predicted FEV1. B) Interaction between PM2.5 from industry and rs1136451 on %predicted FVC. C) Interaction between PM2.5 from marine traffic and rs4253527 on FEV1. D) Interaction between PM2.5 from marine traffic and rs4253527 on predicted FVC.E) Interaction between PM2.5 from marine traffic and rs1059057 on %predicted FVC. Blue lines represent effects on minor allele carriers.FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PM, particle matter.

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 % 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 % 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 % 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 (online supplemental table S1), total PM_{10} and $PM_{2.5}$ were not significantly associated with reductions in % 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 (eg, figure 1).

For GSTP and GSTT genotypes, carrying the minor or null allele was associated with decreased % predicted FEV_1 and FVC, whereas no direct effects of SP-ASNPS were found (online supplemental 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 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 to socioeconomic distribution of the study population in some urban areas, where high-exposed areas also have a high proportion of individuals with high socioeconomic 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 with those presented in the study from Adam *et al*, reporting significant associations for both FEV_1 and FVC in adults related to long-term exposure to NO_2, NO_x and PM_{10}, but not $PM_{2.5}$ or coarse PM in a meta-analysis of the ESCAPE (European Study of Cohorts for Air Pollution Effects) data.[7] In our study, both of NO_x 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 NO_x 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 *et al*,[8] only traffic, and not industry-specific particles, were associated with the lung damage marker CC16. Krall and Strickland[13] observed only effects from tailpipe exhaust on lung function and eNO. Billet *et al*[9] exposed cells in vitro to particles from a highly industrialised environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response. Peng *et al*[6] observed that PM from vehicle emissions, diesel engines and wood burning was associated with the largest increases in emergency hospital admissions for cardiovascular- and respiratory disease.[6] In a multicity 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 PM from the lungs by opsonisation[22] and is activated in response to exposure to ozone, another major air pollutant.[42] The 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 chronic obstructive pulmonary disease (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 provide 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. Non-participation 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 LLN 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 that provides a fair picture of the actual exposure. The resulting, and likely non-differential, 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} (online supplemental 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 multipollutant models, meaning that 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.

Contributors 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 sections and the final manuscript. DS provided and documented the particle matter exposure data. All authors approved the final version of the manuscript and contributed to the discussion.

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Patient consent for publication Obtained.

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