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# BMJ Open

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

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Lung function and PM species data from SCAC

**1 Title page**

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6 2 Traffic related particle matter exposure, lung function effects and potential interactions in a cohort  
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8 3 study  
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**18 Keywords:**

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

21 **ABSTRACT**

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

26 **design:** Cohort study with address-based annual PM exposure assigned from annual estimates of  
27 size (PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub>) and source-specific (traffic, industry, marine traffic and wood burning)  
28 dispersion modelling.

29 **setting:** Gothenburg, Sweden.

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

34 **primary and secondary outcome measures:** The primary outcome was forced vital capacity  
35 (FVC) and forced expiratory flow in 1 second (FEV<sub>1</sub>). The secondary outcome measure was effects  
36 and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

37 **results:** Exposure to traffic-related PM<sub>10</sub> and PM<sub>2.5</sub> was associated with decreases in percent-  
38 predicted FEV<sub>1</sub> by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per  
39 interquartile range (IQR), respectively, and with decreases in percent-predicted FVC by -0.46%  
40 (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM<sub>BC</sub>  
41 was strongly associated with both FEV<sub>1</sub> and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43%  
42 (95%CI -0.77 to -0.09%), respectively, for FVC, and similarly for FEV<sub>1</sub>. Minor allele carrier status  
43 for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-  
44 predicted lung function. Three SP-A SNPs showed effect modification with exposure to PM<sub>2.5</sub> from  
45 industry and marine traffic.

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3 47 **conclusions:** PM exposure, specifically traffic-related, was associated with FVC and FEV<sub>1</sub>  
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5 48 reductions and not modified by genotype. Genetic effect modification was suggested for industry  
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7 49 and marine traffic PM<sub>2.5</sub>.

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10 50 **Article summary:** Strength and limitations of this study

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13 51 • An extensive dispersion model of source-specific PM was assigned to a large, general  
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15 52 population cohort of adults in a single urban region
- 16  
17 53 • The cohort was designed with focus on respiratory health and many covariates were collected  
18  
19 54 as well as genotyping for genes with known associations with respiratory health
- 20  
21 55 • Data collection was performed according to a standardized maneuver by trained personnel  
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23 56 although spirometry was not performed with reversibility test
- 24  
25 57 • Residential history was not available, so exposure is only assigned for the time of inclusion  
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27 58 into the study, which also does not take indoor or occupational air pollution into account.  
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## INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function<sup>1 2</sup> and accelerated lung function decline.<sup>3</sup> However, evidence on specific importance of different particle sizes and sources is still limited,<sup>4</sup> and are to date addressed in only few epidemiological studies of respiratory health effects with non-conclusive results.<sup>2 5 6</sup> 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<sup>7</sup>, 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.<sup>8</sup> 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.<sup>9</sup>

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 NO<sub>x</sub> and ultrafine particles, whereas particles from petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and lanthanum.<sup>10</sup> Particles from other industry is characterized by high levels of trace metals vanadium and nickel,<sup>10 11</sup> 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.<sup>12</sup>

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.<sup>13 14</sup> Glutathione S-transferase (GST) enzymes are involved in metabolizing reactive oxygen species to reduce oxidative stress.<sup>15</sup> GSTP1 SNPs have been reported to modify the risk of cardiovascular disease associated with exposure to NO<sub>2</sub><sup>16</sup> and modify the association between NO<sub>2</sub> and

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3 lung function decline in adults,<sup>17</sup> but findings are inconsistent and no meta-analysis has been  
4 performed.<sup>18 19</sup> Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli  
5 and has important functions in the innate immune system of the lungs, especially for opsonizing  
6 inhaled material.<sup>20</sup> SNPs in SP-A coding regions have been associated with multiple respiratory  
7 diseases,<sup>13 21</sup> and suggested gene-environment interactions for smoking and chronic obstructive  
8 pulmonary disease.<sup>22</sup>  
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12 Many questions remain as to what components of air pollution are harmful in a general population, in  
13 particular at relatively low pollution exposures, and if such associations are modified by genetic factors.  
14 Thus, the aim of the current study was to investigate the effects of different PM sources on lung  
15 function in a general population cohort using epidemiological methods and to investigate lung function  
16 effects of genotype and gene-environment interaction with source-specific particle exposures.  
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## 19 **METHODS**

### 20 **Study population**

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

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

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45 Dynamic spirometry including FEV<sub>1</sub> and FVC was performed with the subject in a sitting position using  
46 a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire,  
47 Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.<sup>30</sup> A local  
48 reference material was used for calculation of percent predicted (% predicted) of FEV<sub>1</sub> and FVC and  
49 lower limit of normal, (LLN, the lower 5<sup>th</sup> percentile in healthy individuals) for FEV<sub>1</sub> and FVC.<sup>31 32</sup>  
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51 Asthma was defined as reporting having had at least one asthma attack in the previous 12 months,  
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3 and atopy was defined as having a positive phadiatop test. We used FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC below  
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5 LLN as an indicator of clinically significant lung function reductions or air flow limitation.  
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9 Based on questionnaire replies, smoking status was categorised into current, former (no smoking  
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11 during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles  
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13 within residential regions, postcodes were categorised into four regions: Inner city, non-central city,  
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15 suburban, and outer suburb or rural. Education was categorised in six categories: elementary school,  
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17 lower secondary school, training or girls' school, grammar school, university, and "other" or not  
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19 reported. Individuals who did not have information on the variables of interest were excluded, except  
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21 for genotype, where analyses were run separately for each SNP. For this study we used genotype data  
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23 on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs and three SP-A2 SNPs.  
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25 All SNPs were coded using a dominant model for the minor (least common) allele. Individuals with self-  
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27 reported non-European background were excluded from the analysis (n=315).  
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### 31 **Statistical methods**

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34 First, descriptive statistics were calculated for the cohort and exposure data, and correlations between  
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36 the total and source-specific exposure estimates for all PM size fractions were determined.  
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40 We estimated the association between each PM size fraction for each PM source, with FEV<sub>1</sub> and FVC,  
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42 in linear models. First, lung function effects associated with PM size fractions and sources were  
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44 analysed with exposure as a continuous variable, and estimated for an interquartile increase in  
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46 exposure. Second, we investigated the effects of the highest exposure values by setting high exposure  
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48 cutoff for PM above the 90<sup>th</sup> percentile of population exposure, medium exposure at 50-90<sup>th</sup>  
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50 percentile, with exposure at or below 50<sup>th</sup> percentile as the reference, and tested these for linear  
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52 trends. To investigate clinically significant effects, we modelled increased risk of low lung function in  
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54 logistic models with LLN as a cut-off. To assess confounding, covariates were added to regression  
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56 models and were retained if the estimate of the main effect was altered by more than 10% by their  
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58 inclusion. The covariates included in the final models were age, sex, weight, education, residential  
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3 postcode region, smoking status, and exposure to passive smoking in the last 12 months. For genetic  
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5 markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes  
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7 and lung function for all available SNPs in single-SNP linear models. To evaluate effect modification,  
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9 we tested for interaction of the effects of exposure to different PM size fractions and sources on lung  
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11 function by genotype, using a likelihood ratio tests comparing the model with interaction term to the  
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13 model without this term. Similarly, the analyses of PM effects were also stratified by sex and  
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15 respiratory health status as well as smoking status, asthma status, atopic status, BMI, age categories  
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17 to evaluate possible confounding from any of these characteristics.  
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21 All regression results for change in lung function were reported as increment or decrement in %  
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23 predicted. Odds ratios were obtained from the logistic model analyses. All results are presented as  
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25 point estimates with 95% confidence intervals, and with p-values as appropriate. Analyses were  
26  
27 performed in R studio<sup>33</sup> using the package “phia” (post-hoc interaction analysis).<sup>34</sup>  
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## 30 31 32 **RESULTS**

33  
34 The ADONIX cohort includes 6685 individuals, of which 5216 were included with information on the  
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36 variables related to exposure and health outcomes used in this study and self-reported European  
37  
38 ancestry. The mean age of the study population was 51.6 ±11.4 years and 46.5% were males, 46.1%  
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40 had never smoked, 16.5% were current smokers and 10.2% were exposed to passive smoking. A total  
41  
42 of 9.5% of individuals had FEV<sub>1</sub> below lower limit of normal and 9.5% had FVC below LLN. The most  
43  
44 common highest education level was university education (37.1%), followed by grammar school  
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46 (23.0%) (Table 1).  
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51 **TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION**

52 N=5216		
53		
54		
55	Age, mean (SD)	51.6 (11.4)
56	Males, n (%)	2427 (46.5%)
57	<b>Females</b>	2789 (53.5%)
58		
59	<b>Respiratory health</b>	
60		

FEV <sub>1</sub> (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV <sub>1</sub> , n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV <sub>1</sub> /FVC, n (%)	548 (10.5%)
<b>Smoking</b>	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)
<b>Passive smoking (last 12 months)</b>	534 (10.2%)
<b>Education</b>	
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%)
<b>Residential area</b>	
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<sub>1</sub>, 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<sup>3</sup> PM<sub>10</sub>, 9.3 µg/m<sup>3</sup> PM<sub>2.5</sub>, and 0.76 µg/m<sup>3</sup> PM<sub>BC</sub> (Table 2). Background long-range transport constituted the main source of exposure, contributing to 75% and 76% of PM<sub>10</sub> and

PM<sub>2.5</sub> levels respectively. The local emission source that contributed most to total PM<sub>10</sub> was traffic, whereas residential heating contributed most to PM<sub>2.5</sub> (Table 2).

**TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION**

PM species and sources	Mean (standard deviation)	50 <sup>th</sup> percentile	90 <sup>th</sup> percentile	IQR
<u>PM<sub>10</sub> total</u>	15.7 (2.49)	15.47	18.80	3.05
Traffic (µg/m <sup>3</sup> )	2.32 (1.75)	1.78	4.41	1.64
Residential heating (µg/m <sup>3</sup> )	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (µg/m <sup>3</sup> )	0.03 (0.05)	0.02	0.08	0.03
Industry (µg/m <sup>3</sup> )	0.11 (0.09)	0.09	0.23	0.10
<u>PM<sub>2.5</sub> total</u>	9.33 (1.75)	9.36	11.80	2.47
Traffic (µg/m <sup>3</sup> )	0.74 (0.56)	0.57	1.41	0.52
Residential heating (µg/m <sup>3</sup> )	1.22 (0.48)	1.17	1.88	0.62
Marine traffic (µg/m <sup>3</sup> )	0.03 (0.05)	0.05	0.08	0.03
Industry (µg/m <sup>3</sup> )	0.07 (0.05)	0.06	0.12	0.06
<u>PM<sub>BC</sub> total</u>	0.76 (0.32)	0.71	1.13	0.33
Traffic (µg/m <sup>3</sup> )	0.36 (0.29)	0.27	0.69	0.25
Residential heating (µg/m <sup>3</sup> )	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (µg/m <sup>3</sup> )	0.01 (0.01)	0.00	0.02	0.01
Industry (µg/m <sup>3</sup> )	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		p-value	B	95% CI		p-value
		Lower	Upper			Lower	Upper	
<b><math>PM_{10}</math> Total</b>	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	<b>-0.48</b>	<b>-0.89</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.46</b>	<b>-0.83</b>	<b>-0.08</b>	<b>0.02</b>
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
<b><math>PM_{2.5}</math> Total</b>	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	<b>-0.47</b>	<b>-0.88</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.47</b>	<b>-0.83</b>	<b>-0.10</b>	<b>0.01</b>
Residential heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91

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2									
3	heating								
4									
5	Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
6	Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
7									
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10	<b>PM<sub>BC</sub> Total</b>	<b>-0.56</b>	<b>-1.01</b>	<b>-0.12</b>	<b>0.01</b>	<b>-0.53</b>	<b>-0.94</b>	<b>-0.13</b>	<b>0.01</b>
11	Traffic	-0.41	-0.78	-0.03	0.03	<b>-0.43</b>	<b>-0.77</b>	<b>-0.09</b>	<b>0.01</b>
12	Residential								
13	heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
14									
15	Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
16	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<sub>1</sub> ( $p$  for trend<0.05; for FEV<sub>1</sub> and PM<sub>BC</sub> 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<sub>1</sub> 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<sub>1</sub> and FVC ( $p<0.05$ ; except  $p=0.08$  for FEV<sub>1</sub> and PM<sub>BC</sub>) (Table S5). FEV<sub>1</sub>/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<sub>1</sub> reductions by -0.80% ( $p=0.044$ ) and -0.90%

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

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13 PM<sub>2.5</sub>, which had marginally more consistent effects for traffic-related exposure, was used for  
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15 interaction analyses. The effect of genotype and exposure to PM<sub>2.5</sub> from all sources was analysed in  
16  
17 interaction models, and SNPs with exposure-interaction p-values lower than 0.1 are shown in Table  
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19 S2. The number of significant interactions was higher than expected by chance. The most plausible  
20  
21 statistically significant patterns of interaction were seen for industry-related exposure (Figure 2). Two  
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23 SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV<sub>1</sub> and FVC,  
24  
25 and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result should,  
26  
27 however, be seen as highly exploratory. Stratifying data by smoking status, atopy, asthma status, and  
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29 BMI category showed no effect modification on the estimates for air pollution effects in both linear  
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31 and logistic analysis (data not shown).  
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## DISCUSSION

In a general population cohort exposed to moderate levels of PM air pollution in a global perspective, modelled exposure to PM<sub>10</sub> and PM<sub>2.5</sub> from traffic, as well as PM<sub>BC</sub> were associated with reductions in FVC and FEV<sub>1</sub> in linear models, a pattern also consistently shown for high exposure in analyses with categorized exposure, and for risk of reduced FEV<sub>1</sub> or FVC (below LLN) in logistic regression. We observed no associations for airflow limitation (FEV<sub>1</sub>/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.<sup>27</sup>

In the current study, we found the most consistent associations between both FEV<sub>1</sub> 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<sub>2.5</sub> from residential heating, marine traffic or industry on FEV<sub>1</sub> 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.<sup>13</sup> 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<sub>10</sub> and PM<sub>2.5</sub> were not significantly associated with FVC and FEV<sub>1</sub>, although the direction of effect

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3 was consistent with that from traffic PM<sub>10</sub> and PM<sub>2.5</sub>. Residential heating is the second largest local  
4 contribution to total PM, and we observed negative correlations between PM from residential heating  
5 and total PM as well as PM from other sources. PM from residential heating might thus be interpreted  
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7 as an indicator of low exposure to other sources of air pollution which might contribute to explaining  
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9 the few suggested inverse (positive) associations seen in some categorical analyses between PM from  
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11 residential heating and FEV<sub>1</sub> and FVC (e.g. Figure 1).  
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18 In a previous study of the same cohort material, short distance to the nearest road was found to be  
19 associated with decreases in FEV<sub>1</sub> and FVC.<sup>35</sup> The pollution levels found in the current study were  
20 moderate compared to those presented in the study from Adam and colleagues.<sup>6</sup> In a meta-analysis of  
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22 the ESCAPE data, that study found significant associations for both FEV<sub>1</sub> and FVC in adults related to  
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24 long-term exposure to NO<sub>2</sub>, NO<sub>x</sub> and PM<sub>10</sub>, but not PM<sub>2.5</sub> or coarse PM. In our data, modelled annual  
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26 averages of NO<sub>x</sub> and NO<sub>2</sub> were available for parts of the cohort for some years, and both were highly  
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28 correlated with traffic PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (all correlations r>0.79).  
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34 Effects specifically of exposure to industrial emissions has not been widely studied, and industry  
35 emissions are often pooled with other sources,<sup>27</sup> or considered negligible as high stacks disperse the  
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37 emissions.<sup>36</sup> Studies of respiratory health with source specific results generally find associations mainly  
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39 with traffic: In the study of Jacquemin and colleagues,<sup>7</sup> only traffic, and not industry-specific particles  
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41 were associated with the lung damage marker CC16. Krall and colleagues<sup>9</sup> observed only effects from  
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43 tailpipe exhaust on lung function and eNO. Billet and colleagues<sup>8</sup> exposed cells *in-vitro* to particles from  
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45 a highly industrialized environment and found that ultrafine particles with higher concentrations of  
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47 polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response.  
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49 Peng and colleagues<sup>5</sup> observed that PM from vehicle emissions, diesel engines and wood burning were  
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51 associated with the largest increases in emergency hospital admissions for CVD and respiratory  
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53 disease.<sup>5</sup> In a multi-city European study<sup>37</sup> there were negative associations between FEV<sub>1</sub> and PM from  
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3 nickel and sulphur, however results were not consistent between cities, perhaps reflecting the  
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5 heterogeneity in particle compositions in different cities in the study.<sup>38</sup>  
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9 For the two SP-A1 SNPs that had potential interactions of interest with industry PM in our study, other  
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11 studies have found rs1059057 to be associated with lung injury<sup>39</sup> and cystic fibrosis,<sup>40</sup> and rs1136451  
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13 with susceptibility to COPD,<sup>22</sup> but only gene-environment effects from tobacco smoking were  
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15 addressed in these studies. GSTP1 SNP rs1695 was previously associated with possible increased  
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17 asthma risk of air pollution exposure,<sup>18</sup> and we found a main effect associated with lower FEV<sub>1</sub> in the  
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19 current study of adults. These genetic results should be seen as exploratory and be interpreted with  
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21 caution.  
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25 The cohort data used in this study were collected to study respiratory health, and provides a rich  
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27 dataset containing a large number of variables of interest. In the model selection, adding additional  
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29 covariates as potential confounders did not affect the regression estimates substantially.  
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31 Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered  
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33 2001–2003) and showed that women, the elderly, and individuals with university education were more  
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35 likely to participate.<sup>26</sup> As we adjusted for these covariates and as exposure was unknown to  
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37 participants, this is not very likely to bias the current results.  
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41 The number of individuals who fell below the lower limit of normal for both FEV<sub>1</sub> and FVC was rather  
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43 high, as this value is defined as the 5<sup>th</sup> percentile in a healthy, non-smoking population. It is possible  
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45 that individuals with respiratory issues are more likely to take part in a study such as ADONIX. On the  
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47 other hand, with clinical outcome measures and an exposure which was not known to the participants,  
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49 this is an unlikely source of important bias.  
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53 In this study, complete residential histories, including duration of residence, were not available.  
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55 Instead, we used a single modelled value for residential exposure that was matched by year of  
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57 participation for each individual, rather than a complete longitudinal exposure history over multiple  
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3 years. We consider this a reasonable approach, as the between-year correlation in air pollution  
4 concentrations and emissions in a certain location is very high.  
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8 As people spend a sizable proportion of their time outside the home, our results are based on modelled  
9 air pollution data, and thus represents an approximation of the real exposure although this is an  
10 established method. The resulting misclassification of exposure would, however, then to reduce risk  
11 estimates. The model was developed using new emissions inventories, updated information on vehicle  
12 composition, and had been further verified by measurements.<sup>27</sup> However, for residential heating, the  
13 source assignment is based on proxies such as building type, as no actual source inventory was  
14 available.  
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25 The very high correlations between traffic-related PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (Table S3) mean that it is  
26 difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to  
27 high correlations between the various PM source measures also meant we had to refrain from using  
28 multi-pollutant models, meaning that interpretation of estimates associated with each exposure type  
29 must be interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent  
30 associations with FEV<sub>1</sub> and FVC, whereas the other source-specific exposures did not.  
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## 39 CONCLUSION

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42 In this large study of clinically measured outcomes in a general population sample we found that  
43 exposure to traffic particles of all three studied size fractions was associated with reductions in FEV<sub>1</sub>  
44 and FVC and increased risk of low FEV<sub>1</sub> and FVC (below LLN), supporting the need for measures to  
45 reduce urban pollution from traffic to protect urban populations. Furthermore, we found intriguing  
46 suggestions that the SP-A1 gene may play a part in susceptibility to air pollution from industrial  
47 sources, possibly due to its very different composition.  
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### 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<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50<sup>th</sup> to 90<sup>th</sup>) and high (above 90<sup>th</sup> percentile) concentration of source-specific PM

Figure 2 a-e Gene-environment interactions of selected SNPs and FEV<sub>1</sub> and FVC in exposure categories to select PM sources. Dotted lines represent effects on minor allele carriers

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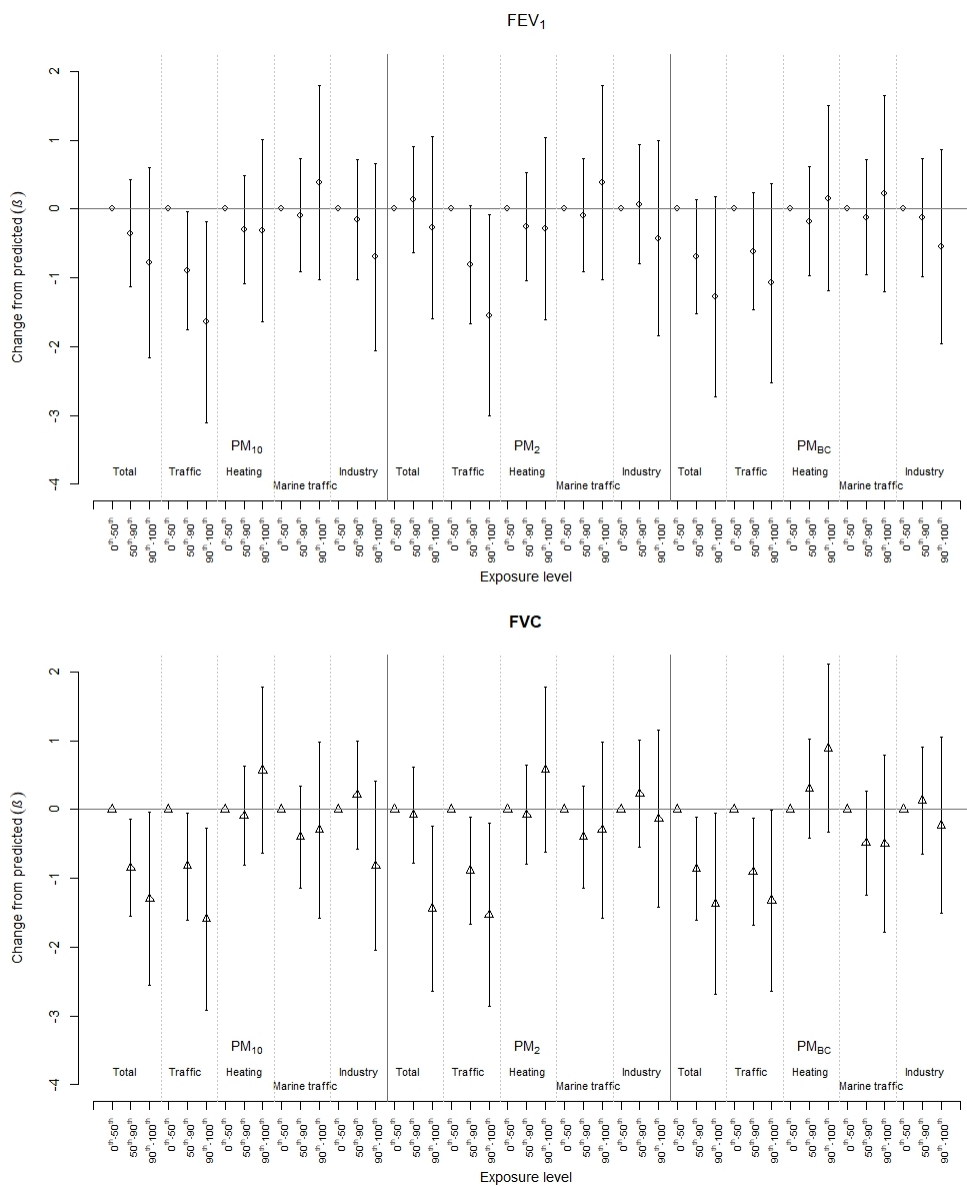
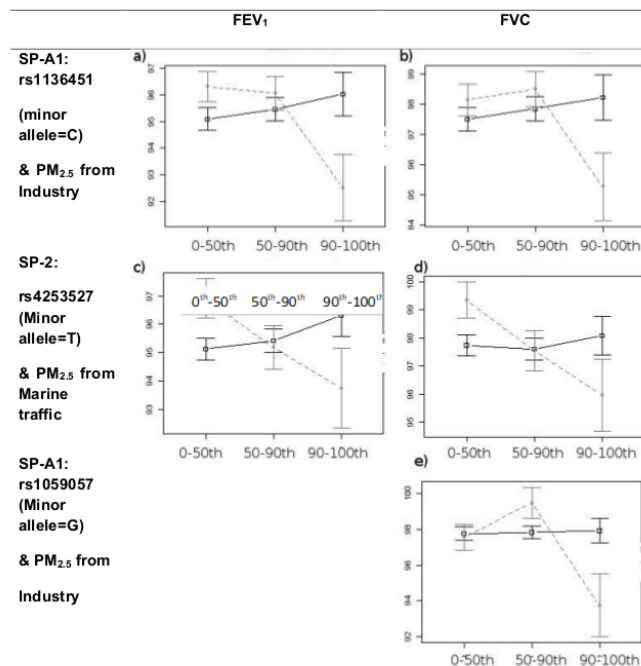


Figure 1 Change in FEV<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

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)

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Lung function and PM species data from SCAC

**1 Title page**

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

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17 **Word count: 3506**

**18 Keywords:**

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

21 **ABSTRACT**

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

26 **design:** Cohort study with address-based annual PM exposure assigned from annual estimates of  
27 size (PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub>) and source-specific (traffic, industry, marine traffic and wood burning)  
28 dispersion modelling.

29 **setting:** Gothenburg, Sweden.

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

34 **primary and secondary outcome measures:** The primary outcome was forced vital capacity  
35 (FVC) and forced expiratory flow in 1 second (FEV<sub>1</sub>). The secondary outcome measure was effects  
36 and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

37 **results:** Exposure to traffic-related PM<sub>10</sub> and PM<sub>2.5</sub> was associated with decreases in percent-  
38 predicted FEV<sub>1</sub> by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%) per  
39 interquartile range (IQR), respectively, and with decreases in percent-predicted FVC by -0.46%  
40 (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%). Total and traffic-related PM<sub>BC</sub>  
41 was strongly associated with both FEV<sub>1</sub> and FVC by -0.53 (95%CI -0.94 to -0.13%) and -0.43%  
42 (95%CI -0.77 to -0.09%), respectively, for FVC, and similarly for FEV<sub>1</sub>. Minor allele carrier status  
43 for two GSTP1 SNPs and the GSTT1 null genotype were associated with decreases in percent-  
44 predicted lung function. Three SP-A SNPs showed effect modification with exposure to PM<sub>2.5</sub> from  
45 industry and marine traffic.

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3 47 **conclusions:** PM exposure, specifically traffic-related, was associated with FVC and FEV<sub>1</sub>  
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5 48 reductions and not modified by genotype. Genetic effect modification was suggested for industry  
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7 49 and marine traffic PM<sub>2.5</sub>.

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10 50 **Article summary:** Strength and limitations of this study

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13 51 • An extensive dispersion model of source-specific PM was assigned to a large, general  
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15 52 population cohort of adults in a single urban region
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17 53 • The cohort was designed with focus on respiratory health and many covariates were collected  
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19 54 as well as genotyping for genes with known associations with respiratory health
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21 55 • Data collection was performed according to a standardized maneuver by trained personnel  
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23 56 although spirometry was not performed with reversibility test
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25 57 • Residential history was not available, so exposure is only assigned for the time of inclusion  
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27 58 into the study, which also does not take indoor or occupational air pollution into account.  
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## INTRODUCTION

Exposure to air pollution, especially traffic-related air pollution, is associated with reduced lung function<sup>1,2</sup> and accelerated lung function decline.<sup>3</sup> However, evidence on specific importance of different particle sizes and sources is still limited,<sup>4</sup> and are to date addressed in only few epidemiological studies of respiratory health effects with non-conclusive results.<sup>2,5,6</sup> 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<sup>7</sup>, 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.<sup>8</sup> 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.<sup>9</sup>

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.<sup>10</sup> Particles from other industry is characterized by high levels of trace metals vanadium and nickel,<sup>10</sup> 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.<sup>12</sup> 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.<sup>13,14</sup> Glutathione S-transferase (GST) enzymes are involved in metabolizing reactive oxygen species to reduce oxidative stress.<sup>15</sup> GSTP1 SNPs have been reported

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3 to modify the risk of cardiovascular disease associated with exposure to NO<sub>2</sub><sup>16</sup> and modify the association between NO<sub>2</sub> and lung function decline in adults,<sup>17</sup>  
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5 but findings are inconsistent and no meta-analysis has been performed.<sup>18-19</sup> Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung  
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7 alveoli and has important functions in the innate immune system of the lungs, especially for opsonizing inhaled material.<sup>20</sup> SNPs in SP-A coding regions have  
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9 been associated with multiple respiratory diseases,<sup>13-21</sup> and suggested gene-environment interactions for smoking and chronic obstructive pulmonary  
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11 disease.<sup>22</sup>

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15 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  
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17 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  
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19 a general population cohort using epidemiological methods and to investigate lung function effects of genotype and gene-environment interaction with  
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21 source-specific particle exposures.  
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## 23 24 25 **METHODS**

### 26 27 28 **Study population**

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31 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  
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33 invited to participate in a clinical examination between 2001-2008 as previously described.<sup>16-23-26</sup> In brief, the overall participation rate was 46%, all participants  
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35 provided data on residential address, lifestyle factors and education, presence of allergic airway inflammation and respiratory health, as well as clinical  
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3 measurements of lung function, such as spirometry (single manoeuvre) and nitric oxide in exhaled air (FENO). Blood samples were collected for DNA extraction  
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5 and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1 genes.  
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## 8 **Exposure assessment**

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11 As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish Meteorological and Hydrological Institute (SMHI) modelled  
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13 source-specific, annual particulate matter (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using dispersion  
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15 modelling described in detail in Segersson and colleagues.<sup>27</sup> PM<sub>10</sub> and PM<sub>2.5</sub> represent particles smaller than 10 and 2.5 micrometers (µm) respectively,  
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17 whereas black carbon particles, PM<sub>BC</sub>, are soot particles from combustion, notably vehicle exhaust. The specific sources were traffic (exhaust and road wear  
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19 for PM<sub>10</sub> and PM<sub>2.5</sub>, exhaust only for PM<sub>BC</sub>), residential heating (predominantly house heating using wood assessed as area sources), marine traffic (averaged  
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21 description from a bottom-up calculation using actual positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in  
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23 Gothenburg dominated by refineries, energy plants, and other industry).<sup>28</sup> Background concentration (long-range transport particles), was also provided, but  
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25 was estimated indirectly as the difference between total modelled local contribution and monitoring data from a central urban background station.  
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27 Consequently, it showed no spatial variation and was not used for analyses. To refine the estimated contribution of traffic, an increment due to reduced  
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29 ventilation in the street canyons was added for the busiest streets. The increment was estimated as the difference between simulations with and without  
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31 buildings using the OSPM model.<sup>29</sup> For each study participant's residential address at the date of clinical examination, annual mean values of pollutants were  
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33 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  
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35 examination.  
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## Outcome definitions

Dynamic spirometry including FEV<sub>1</sub> 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.<sup>30</sup> A local reference material was used for calculation of percent predicted (% predicted) of FEV<sub>1</sub> and FVC and lower limit of normal, (LLN, the lower 5<sup>th</sup> percentile in healthy individuals) for FEV<sub>1</sub> and FVC.<sup>31 32</sup> 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<sub>1</sub>, FVC and FEV<sub>1</sub>/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



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3 First, descriptive statistics were calculated for the cohort and exposure data, and correlations between the total and source-specific exposure estimates for  
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5 all PM size fractions were determined.  
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8 We estimated the association between each PM size fraction for each PM source, with FEV<sub>1</sub> and FVC, in linear models. First, lung function effects associated  
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10 with PM size fractions and sources were analysed with exposure as a continuous variable, and estimated for an interquartile increase in exposure. Second, we  
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12 investigated the effects of the highest exposure values by setting high exposure cutoff for PM above the 90<sup>th</sup> percentile of population exposure, medium  
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14 exposure at 50-90<sup>th</sup> percentile, with exposure at or below 50<sup>th</sup> percentile as the reference, and tested these for linear trends. To investigate clinically significant  
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16 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  
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18 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  
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20 age, sex, weight, education, residential postcode region, smoking status, and exposure to passive smoking in the last 12 months. For genetic markers, we  
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22 assessed Hardy-Weinberg equilibrium, then analysed the association between genotypes and lung function for all available SNPs in single-SNP linear models.  
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24 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,  
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26 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  
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28 stratified by sex and respiratory health status as well as smoking status, asthma status, atopic status, BMI, age categories to evaluate possible confounding  
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30 from any of these characteristics.  
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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<sup>33</sup> using the package “phia” (post-hoc interaction analysis).<sup>34</sup>

## 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<sub>1</sub> 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%)
<b>Females</b>	2789 (53.5%)
<b>Respiratory health</b>	
FEV <sub>1</sub> (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV <sub>1</sub> , n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)

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3 Below LLN of FEV<sub>1</sub>/FVC, n (%) 548 (10.5%)  
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5 **Smoking**

6 Current smokers, n (%) 860 (16.5%)  
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8 Former smokers, n (%) 1951 (37.4%)  
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10 Never smokers, n (%) 2405 (46.1%)  
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12 **Passive smoking (last 12 months)** 534 (10.2%)  
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14 **Education**

15 Elementary school, n (%) 639 (12.2%)  
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17 Lower secondary School, n (%) 175 (3.3%)  
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19 Training/girls school, n (%) 389 (7.5%)  
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21 Grammar school, n (%) 1205 (23.1%)  
22

23 University, n (%) 1954 (37.5%)  
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25 Other or not reported, n (%) 853 (16.4%)  
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27 **Residential area**

28 Inner city, n (%) 945 (18.1%)  
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30 Non-central urban, n (%) 922 (17.7%)  
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32 Suburban, n (%) 2178 (41.7%)  
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34 Outer suburb or rural, n (%) 1171 (22.4%)  
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36 \*Lung function predicted from age, height and sex (Brisman et al., 2017) FEV<sub>1</sub>, forced  
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38 expiratory volume in 1 second.  
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40 FVC, forced vital capacity.  
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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  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ , 9.3  $\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ , and 0.76  $\mu\text{g}/\text{m}^3$   $\text{PM}_{\text{BC}}$  (Table 2). Background long-range transport constituted the main source of exposure, contributing to 75% and 76% of  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  levels respectively. The local emission source that contributed most to total  $\text{PM}_{10}$  was traffic, whereas residential heating contributed most to  $\text{PM}_{2.5}$  (Table 2).

**TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY POPULATION**

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

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PM <sub>BC</sub> total (µg/m <sup>3</sup> )	0.76 (0.32)	0.71	1.13	0.33
Traffic (µg/m <sup>3</sup> )	0.36 (0.29)	0.27	0.69	0.25
Residential heating(µg/m <sup>3</sup> )	0.14 (0.06)	0.13	0.23	0.06
Marine traffic (µg/m <sup>3</sup> )	0.01 (0.01)	0.00	0.02	0.01
Industry (µg/m <sup>3</sup> )	0.01 (0.01)	0.01	0.01	0.01

IQR, interquartile range.

Traffic was the largest contributor to PM<sub>BC</sub>, and for PM<sub>BC</sub> the contribution from long-range sources was considerably lower than for PM<sub>10</sub> and PM<sub>2.5</sub>, 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<sub>BC</sub> ( $r = .99$ ), whereas it was high for PM<sub>10</sub> ( $r = .75$ ) and moderate for PM<sub>2.5</sub> ( $r = .40$ ) (Table S3).

### Effects of PM exposure

Most PM sources were negatively associated with percent predicted lung function, and estimates for PM<sub>BC</sub> overall and from traffic, and for PM<sub>2.5</sub> and PM<sub>10</sub> from traffic, reached statistical significance for reductions in FEV<sub>1</sub> 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<sub>1</sub> AND FVC PER IQR CHANGE IN PM FROM DIFFERENT SOURCES

	Delta % predicted FEV <sub>1</sub>				Delta % predicted FVC			
	B	95% CI		p-value	B	95% CI		p-value
		Lower	Upper			Lower	Upper	
<b>PM<sub>10</sub> Total</b>	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	<b>-0.48</b>	<b>-0.89</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.46</b>	<b>-0.83</b>	<b>-0.08</b>	<b>0.02</b>
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
<b>PM<sub>2.5</sub> Total</b>	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	<b>-0.47</b>	<b>-0.88</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.47</b>	<b>-0.83</b>	<b>-0.10</b>	<b>0.01</b>
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
<b>PM<sub>10</sub>bc Total</b>	<b>-0.56</b>	<b>-1.01</b>	<b>-0.12</b>	<b>0.01</b>	<b>-0.53</b>	<b>-0.94</b>	<b>-0.13</b>	<b>0.01</b>
Traffic	-0.41	-0.78	-0.03	0.03	<b>-0.43</b>	<b>-0.77</b>	<b>-0.09</b>	<b>0.01</b>
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<sub>1</sub> ( $p$  for trend < 0.05; for FEV<sub>1</sub> and PM<sub>BC</sub> 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<sub>1</sub> 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<sub>1</sub> and FVC ( $p$  < 0.05; except  $p$  = 0.08 for FEV<sub>1</sub> and PM<sub>BC</sub>) (Table S5). FEV<sub>1</sub>/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<sub>1</sub> 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 rs226637 (-1.434%,  $p$  = 0.001). No main effect associations were found with SP-A SNPs (Table S1).

### Effect modification of PM effects

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3 PM<sub>2.5</sub>, which had marginally more consistent effects for traffic-related exposure, was used for interaction analyses. The effect of genotype and exposure to  
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5 PM<sub>2.5</sub> 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  
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7 significant interactions was higher than expected by chance. The most plausible statistically significant patterns of interaction were seen for industry-related  
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9 exposure (Figure 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV<sub>1</sub> and FVC, and on FVC only, respectively,  
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11 suggesting variable susceptibility at high exposures. This result should, however, be seen as highly exploratory. Stratifying data by smoking status, atopy,  
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13 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).  
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## DISCUSSION

In a general population cohort exposed to moderate levels of PM air pollution in a global perspective, modelled exposure to PM<sub>10</sub> and PM<sub>2.5</sub> from traffic, as well as PM<sub>BC</sub> were associated with reductions in FVC and FEV<sub>1</sub> in linear models, a pattern also consistently shown for high exposure in analyses with categorized exposure, and for risk of reduced FEV<sub>1</sub> or FVC (below LLN) in logistic regression. We observed no associations for airflow limitation (FEV<sub>1</sub>/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.<sup>27</sup>

In the current study, we found the most consistent associations between both FEV<sub>1</sub> 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<sub>2.5</sub> from residential heating, marine traffic or industry on FEV<sub>1</sub> 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.<sup>13</sup> Industrial exposure in Gothenburg is concentrated along the Götaälv river and is dominated by a power plant and oil refineries.

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3 In spite moderate to high correlations between the three traffic related PM fractions (Table S3), total PM<sub>10</sub> and PM<sub>2.5</sub> were not significantly associated with  
4 FVC and FEV<sub>1</sub>, although the direction of effect was consistent with that from traffic PM<sub>10</sub> and PM<sub>2.5</sub>. Residential heating is the second largest local contribution  
5 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  
6 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  
7 inverse (positive) associations seen in some categorical analyses between PM from residential heating and FEV<sub>1</sub> and FVC (e.g. Figure 1).  
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12 In a previous study of the same cohort material, short distance to the nearest road was found to be associated with decreases in FEV<sub>1</sub> and FVC.<sup>35</sup> The pollution  
13 levels found in the current study were moderate compared to those presented in the study from Adam and colleagues.<sup>36</sup> In a meta-analysis of the ESCAPE data,  
14 that study found significant associations for both FEV<sub>1</sub> and FVC in adults related to long-term exposure to NO<sub>2</sub>, NO<sub>x</sub> and PM<sub>10</sub>, but not PM<sub>2.5</sub> or coarse PM. In  
15 our data, modelled annual averages of NO<sub>x</sub> and NO<sub>2</sub> were available for parts of the cohort for some years, and both were highly correlated with traffic PM<sub>10</sub>,  
16 PM<sub>2.5</sub> and PM<sub>BC</sub> (all correlations  $r > 0.79$ ).  
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22 Effects specifically of exposure to industrial emissions has not been widely studied, and industry emissions are often pooled with other sources,<sup>27</sup> or considered  
23 negligible as high stacks disperse the emissions.<sup>36</sup> Studies of respiratory health with source specific results generally find associations mainly with traffic: In  
24 the study of Jacquemin and colleagues,<sup>7</sup> only traffic, and not industry-specific particles were associated with the lung damage marker CC16. Krall and  
25 colleagues<sup>9</sup> observed only effects from tailpipe exhaust on lung function and eNO. Billet and colleagues<sup>8</sup> exposed cells *in-vitro* to particles from a highly  
26 industrialized environment and found that ultrafine particles with higher concentrations of polyaromatic hydrocarbons induced more oxidative DNA damage  
27 adducts and DNA damage response. Peng and colleagues<sup>5</sup> observed that PM from vehicle emissions, diesel engines and wood burning were associated with  
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3 the largest increases in emergency hospital admissions for CVD and respiratory disease.<sup>5</sup> In a multi-city European study<sup>37</sup> there were negative associations  
4 between FEV<sub>1</sub> and PM from nickel and sulphur, however results were not consistent between cities, perhaps reflecting the heterogeneity in particle  
5 compositions in different cities in the study.<sup>38</sup>  
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10 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  
11 lung injury<sup>39</sup> and cystic fibrosis,<sup>40</sup> and rs1136451 with susceptibility to COPD,<sup>22</sup> but only gene-environment effects from tobacco smoking were addressed in  
12 these studies. GSTP1 SNP rs1695 was previously associated with possible increased asthma risk of air pollution exposure,<sup>18</sup> and we found a main effect  
13 associated with lower FEV<sub>1</sub> in the current study of adults. These genetic results should be seen as exploratory and be interpreted with caution.  
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20 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.  
21 In the model selection, adding additional covariates as potential confounders did not affect the regression estimates substantially. Nonparticipation analysis  
22 was previously reported for the earliest collected cohort data (gathered 2001–2003) and showed that women, the elderly, and individuals with university  
23 educated were more likely to participate.<sup>26</sup> As we adjusted for these covariates and as exposure was unknown to participants, this is not very likely to bias the  
24 current results.  
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32 The number of individuals who fell below the lower limit of normal for both FEV<sub>1</sub> and FVC was rather high, as this value is defined as the 5<sup>th</sup> percentile in a  
33 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  
34 hand, with clinical outcome measures and an exposure which was not known to the participants, this is an unlikely source of important bias.  
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3 In this study, complete residential histories, including duration of residence, were not available. Instead, we used a single modelled value for residential  
4 exposure that was matched by year of participation for each individual, rather than a complete longitudinal exposure history over multiple years. We consider  
5 this a reasonable approach, as the between-year correlation in air pollution concentrations and emissions in a certain location is very high.  
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10 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  
11 approximation of the real exposure although this is an established method. The resulting misclassification of exposure would, however, then to reduce risk  
12 estimates. The model was developed using new emissions inventories, updated information on vehicle composition, and had been further verified by  
13 measurements.<sup>27</sup> However, for residential heating, the source assignment is based on proxies such as building type, as no actual source inventory was  
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22 The very high correlations between traffic-related PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (Table S3) mean that it is difficult to assign the observed effect to a certain size fraction  
23 with any certainty. The moderate to high correlations between the various PM source measures also meant we had to refrain from using multi-pollutant  
24 models, meaning that interpretation of estimates associated with each exposure type must be interpreted cautiously. Nevertheless, traffic-related PM  
25 exposure showed clear and consistent associations with FEV<sub>1</sub> and FVC, whereas the other source-specific exposures did not.  
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## 32 CONCLUSION

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35 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  
36 was associated with reductions in FEV<sub>1</sub> and FVC and increased risk of low FEV<sub>1</sub> and FVC (below LLN), supporting the need for measures to reduce urban  
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3 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  
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5 pollution from industrial sources, possibly due to its very different composition.  
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### 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<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50<sup>th</sup> to 90<sup>th</sup>) and high (above 90<sup>th</sup> percentile) concentration of source-specific PM

Figure 2 a-e Gene-environment interactions of selected SNPs and FEV<sub>1</sub> 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<sub>1</sub> and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs

	N (%)	FEV <sub>1</sub>				FVC			
		$\beta$	95% CI Lower	95% CI Upper	p	$\beta$	95% CI Lower	95% CI Upper	p
<b>GSTP</b>									
rs1138272 (TT+CT) vs CC	707 (14.3) 4250 (85.7)	0.513	-0.539	1.565	0.339	0.790	-0.161	1.741	0.103
rs596603 (TT+GT) vs GG	3363 (68.0) 1581 (32.0)	-0.336	-1.126	0.455	0.405	-0.216	-0.931	0.499	0.554
rs762803 (AA+AC) vs CC	3309 (67.0) 1633 (33.0)	<b>-0.802</b>	-1.583	-0.02	<b>0.044</b>	<b>-0.736</b>	<b>-1.443</b>	<b>-0.028</b>	<b>0.042</b>
rs1695 (AG+GG) vs AA	2683 (54.4) 2244 (45.5)	<b>-0.902</b>	-1.643	-0.16	<b>0.017</b>	-0.575	-1.246	0.095	0.093
<b>GSTT</b>									
rs2266637 GG vs CC	1005 (23.8) 3219 (76.2)	-0.378	-1.331	0.575	0.437	<b>-1.431</b>	-2.293	-0.57	<b>0.001</b>
<b>SP-A 1</b>									
rs1136450 (CC+GC) vs GG	2926 (63.8) 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)								

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

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**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
<b>FEV<sub>1</sub></b>						
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	<b>rs1136450</b>	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	<b>rs1059046</b>	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
<b>FVC</b>						
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	<b>rs1136450</b>	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	<b>rs1059046</b>	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 <sub>10</sub>					PM <sub>2.5</sub>					PM <sub>BC</sub>				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM <sub>10</sub>	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 <sub>2.5</sub>	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 <sub>BC</sub>	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<sub>1</sub> and FVC (% predicted) across exposure strata from low (0-50<sup>th</sup> percentile) to high (above 90<sup>th</sup> percentile) concentrations of source-specific PM (Figure 1)**

	FEV <sub>1</sub>				FVC			
	$\beta$	95% CI		$p$	$\beta$	95% CI		$p$
		Lower	Upper			Lower	Upper	
<b>PM<sub>10</sub></b>								
Total	-0.37	-0,97	0,22	0.22	<b>-0.73</b>	-1,27	-0,19	<b>0.01</b>
Traffic	<b>-0.85</b>	-1,51	-0,19	<b>0.01</b>	<b>-0.81</b>	-1,40	-0,21	<b>0.01</b>
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
<b>PM<sub>2.5</sub></b>								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	<b>-0.79</b>	-1,45	-0,13	<b>0.02</b>	<b>-0.81</b>	-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
<b>PM<sub>BC</sub></b>								
Total	<b>-0.66</b>	-1,30	-0,01	<b>0.05</b>	-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<sub>1</sub> and FVC below LLN in medium and high exposure strata by PM source and size fraction\***

Model	Percentile	LLN FEV <sub>1</sub>				LLN FVC				
		OR	95% CI		p	OR	95% CI		p	
			lower	upper			lower	upper		
<b>PM<sub>10</sub></b>										
Total	0-50 <sup>th</sup>	-	-	-	-					
	50 <sup>th</sup> -90 <sup>th</sup>	1.05	0.87	1.26	0.61	<b>1.23</b>	<b>1.00</b>	<b>1.51</b>	<b>0.05</b>	
	90 <sup>th</sup> -100 <sup>th</sup>	1.18	0.86	1.62	0.31	<b>1.40</b>	<b>0.98</b>	<b>1.99</b>	<b>0.06</b>	
Traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18	
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.46</b>	<b>1.06</b>	<b>2.02</b>	<b>0.02</b>	<b>1.45</b>	<b>1.00</b>	<b>2.08</b>	<b>0.05</b>	
Residential heating	0-50 <sup>th</sup>	ref	-	-	-		ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87	
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06	
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89	
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64	
Industry	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79	
	90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49	
<b>PM<sub>2.5</sub></b>										
Total	0-50 <sup>th</sup>									
	50 <sup>th</sup> -90 <sup>th</sup>	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77	
	90 <sup>th</sup> -100 <sup>th</sup>	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11	
Traffic	0-50 <sup>th</sup>	ref	-	-	-					
	50 <sup>th</sup> -90 <sup>th</sup>	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09	
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.47</b>	<b>1.06</b>	<b>2.03</b>	<b>0.02</b>	<b>1.54</b>	<b>1.07</b>	<b>2.21</b>	<b>0.02</b>	
Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87	
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06	
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89	
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64	

Industry	0-50 <sup>th</sup>					ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	0.91	0.74	1.12	0.38	1.03	0.82	1.30	0.79
	90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
<b>PM<sub>BC</sub></b>									
Total	0-50 <sup>th</sup>					ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
	90 <sup>th</sup> -100 <sup>th</sup>	1.34	0.97	1.86	0.08	<b>1.46</b>	<b>1.02</b>	<b>2.09</b>	<b>0.04</b>
Traffic	0-50 <sup>th</sup>	ref	-	-	-				
	50 <sup>th</sup> -90 <sup>th</sup>	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
	90 <sup>th</sup> -100 <sup>th</sup>	1.37	0.98	1.90	0.06	<b>1.55</b>	<b>1.08</b>	<b>2.23</b>	<b>0.02</b>
Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
	90 <sup>th</sup> -100 <sup>th</sup>	0.80	0.57	1.11	0.18	<b>0.64</b>	<b>0.44</b>	<b>0.94</b>	<b>0.02</b>
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
	90 <sup>th</sup> -100 <sup>th</sup>	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
Industry	0-50 <sup>th</sup>					ref	-	-	
	50 <sup>th</sup> -90 <sup>th</sup>	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
	90 <sup>th</sup> -100 <sup>th</sup>	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<sub>1</sub>, 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	
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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 definitions
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
<b>Results</b>			
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.
<b>Discussion</b>			
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
<b>Other information</b>			
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.

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

# BMJ Open

## 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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Secondary Subject Heading:	Respiratory medicine, Public health
Keywords:	EPIDEMIOLOGY, GENETICS, PARTICLE MATTER, SURFACTANT PROTEIN A, glutathione S-transferase, LUNG FUNCTION

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2020

Lung function and PM species data from SCAC

**1 Title page**

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

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17 \*Corresponding author, telephone number 0046 766238918

18 **Word count: 3506**

**19 Keywords:**

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

21 **ABSTRACT**

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

26 **design:** Cohort study with address-based annual PM exposure assigned from annual estimates of  
27 size (PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub>) and source-specific (traffic, industry, marine traffic and wood burning)  
28 dispersion modelling.

29 **setting:** Gothenburg, Sweden.

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

34 **primary and secondary outcome measures:** The primary outcome was forced vital capacity  
35 (FVC) and forced expiratory flow in 1 second (FEV<sub>1</sub>). Secondary outcome measure were effects  
36 and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.

37 **results:** Exposure to traffic-related PM<sub>10</sub> and PM<sub>2.5</sub> was associated with decreases in percent-  
38 predicted FEV<sub>1</sub> by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%)  
39 per interquartile range (IQR) 3.05 and 2.47 µg/m<sup>3</sup>, respectively, and with decreases in percent-  
40 predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%).  
41 Total and traffic-related PM<sub>BC</sub> was strongly associated with both FEV<sub>1</sub> and FVC by -0.53  
42 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%) per IQR, respectively, for FVC,  
43 and similarly for FEV<sub>1</sub>. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null  
44 genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs  
45 showed effect modification with exposure to PM<sub>2.5</sub> from industry and marine traffic.

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6 47 **conclusions:** PM exposure, specifically traffic-related, was associated with FVC and FEV<sub>1</sub>  
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8 48 reductions and not modified by genotype. Genetic effect modification was suggested for industry  
9  
10 49 and marine traffic PM<sub>2.5</sub>.

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12  
13 50 **Article summary:** Strength and limitations of this study

- 14  
15  
16 51 • An extensive dispersion model of source-specific PM was assigned to a large, general  
17  
18 52 population cohort of adults in a single urban region
- 19  
20 53 • The cohort was designed with focus on respiratory health and a broad range of covariates  
21  
22 54 were collected as well as genotyping for genes with known associations with respiratory  
23  
24 55 health
- 25  
26 56 • Spirometry was performed according to a standardized maneuver by trained personnel  
27  
28 57 although not with reversibility test
- 29  
30 58 • Full residential history was not available, so exposure is only assigned for the time of inclusion  
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32 59 into the study, which also does not take indoor or occupational air pollution into account.  
33  
34 60 Nevertheless, the population is known to be relatively stable and home address exposure is  
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36 61 commonly used as the main exposure measure for air pollution since this is where people  
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38 62 spend most of their time.  
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## 63 INTRODUCTION

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

74 In epidemiological studies, air pollution is most often assigned to certain sources by building exposure  
75 profiles from particle size distributions and relative concentrations of specific chemicals in the  
76 particles. Traffic pollution is for example characterized by NO<sub>x</sub> and ultrafine particles.<sup>7</sup> Particles from  
77 petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and  
78 lanthanum,<sup>10</sup> and particles from other industry is characterized by high levels of trace metals vanadium  
79 and nickel,<sup>10 11</sup> but are of course sector-dependent. Similarly, PM from marine traffic is subject to large  
80 uncertainties as fuel types and fleet types vary across the world.<sup>12</sup> However, this field of research is  
81 expanding rapidly as exposure science evolves with more sophisticated source specific models.<sup>13</sup>  
82 Beyond the importance of exposure composition and source, individual susceptibility to air pollution  
83 is modified by many factors, including genetic differences. Susceptibility related to genetic variability  
84 may improve our understanding of the physiological mechanisms underlying health effects of air  
85 pollution.<sup>14 15</sup> Glutathione S-transferase (GST) are involved in metabolizing reactive oxygen species to  
86 reduce oxidative stress.<sup>16</sup> GSTP1 SNPs have been reported to modify the risk of cardiovascular disease  
87 associated with exposure to NO<sub>2</sub><sup>17</sup> and to modify the association between NO<sub>2</sub> and lung function

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3 88 decline in adults,<sup>18</sup> but findings are inconsistent and no meta-analysis has been performed.<sup>19,20</sup>  
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5 89 Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has  
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7 90 important functions in the innate immune system of the lungs, especially for opsonizing inhaled  
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10 91 material.<sup>21</sup> SP-A gene polymorphisms are associated with development of serious pulmonary disease  
11  
12 92 and are involved in the pulmonary defence against pathogens.<sup>22</sup> SNPs in SP-A coding regions have been  
13  
14 93 associated with multiple respiratory diseases,<sup>14 23</sup> as well as gene-environment interactions for  
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16 94 smoking and chronic obstructive pulmonary disease.<sup>24</sup>  
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19 95 Many questions remain as to what components of air pollution are harmful in a general population, in  
20  
21 96 particular at relatively low pollution exposures, and if such associations are modified by genetic factors.  
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23 97 Thus, the aim of the current study was to investigate the effects of different PM sources determined  
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25 98 from a state-of the arts dispersion model on lung function in a general population cohort, and to  
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27 99 investigate lung function effects of genotype and gene-environment interaction with particle  
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30 100 exposures types.  
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## 33 101 **METHODS**

### 34 102 **Study population**

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37 103 The study population originates from the ADONIX (ADult-Onset asthma and Nitric oxide) cohort, a  
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39 104 random sample of subjects aged 24-76 years who were invited to participate in a clinical examination  
40  
41 105 between 2001-2008, as previously described.<sup>17 25-28</sup> In brief, the overall participation rate was 46%, all  
42  
43 106 participants provided data on residential address, lifestyle factors and education, presence of allergic  
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46 107 airway inflammation and respiratory health, as well as clinical measurements of lung function, such as  
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48 108 spirometry (single manoeuvre) and nitric oxide in exhaled air (FENO). Blood samples were collected  
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51 109 for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1  
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54 110 genes.  
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### 58 111 **Exposure assessment**

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3 112 As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish  
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5 113 Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter  
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7 114 (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using  
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9  
10 115 dispersion modelling described in detail by Segersson and colleagues, 2017, including a detailed map  
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12 116 of the area.<sup>29</sup> PM<sub>10</sub> and PM<sub>2.5</sub> represent particles smaller than 10 and 2.5 micrometers (µm)  
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14 117 respectively, whereas black carbon particles, PM<sub>BC</sub>, are soot particles from combustion, notably vehicle  
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16 118 exhaust. The specific sources that were investigated were traffic (exhaust and road wear for PM<sub>10</sub> and  
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18 119 PM<sub>2.5</sub>, exhaust only for PM<sub>BC</sub>), residential heating (predominantly house heating using wood assessed  
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20 120 as area sources), marine traffic (averaged description from a bottom-up calculation using actual  
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22 121 positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in  
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24 122 Gothenburg dominated by refineries, energy plants, and other industry).<sup>30</sup> Background concentration  
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26 123 (long-range transport particles), was also provided, but was estimated indirectly as the difference  
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28 124 between total modelled local contribution and monitoring data from a central urban background  
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30 125 station. Consequently, it showed no spatial variation and was not used for analyses. To refine the  
31  
32 126 estimated contribution of traffic, an increment due to reduced ventilation in street canyons was added  
33  
34 127 for the busiest streets. The increment was estimated as the difference between simulations with and  
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36 128 without buildings using the OSPM model.<sup>31</sup> For each study participant's residential address at the date  
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38 129 of clinical examination, annual mean values of pollutants were calculated separately for the five source  
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40 130 categories and modelled exposure grid values of all PM fractions were matched to the year of the  
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42 131 participant's clinical examination.  
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### 132 **Outcome definitions**

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51 133 Dynamic spirometry including FEV<sub>1</sub> and FVC was performed with the subject in a sitting position using  
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53 134 a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyaire,  
54  
55 135 Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.<sup>32</sup> A local  
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57 136 reference material was used for calculation of percent predicted (% predicted) of FEV<sub>1</sub> and FVC and  
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3 137 lower limit of normal, (LLN, the lower 5<sup>th</sup> percentile in healthy individuals) for FEV<sub>1</sub> and FVC.<sup>33 34</sup> Asthma  
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5 138 was defined as reporting having had at least one asthma attack in the previous 12 months, and atopy  
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7 139 was defined as having a positive phadiatop test. We used FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC below LLN as an  
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9 140 indicator of clinically significant lung function reductions or air flow limitation.  
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13 141 Based on questionnaire replies, smoking status was categorised into current, former (no smoking  
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15 142 during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles  
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17 143 within residential regions, postcodes were categorised into four residential areas: Inner city, non-  
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19 144 central city, suburban, and outer suburb or rural. Education was categorised in six categories:  
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21 145 elementary school, lower secondary school, training or girls' school, grammar school, university, and  
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23 146 "other" or not reported. Individuals who did not have information on all variables of interest were  
24  
25 147 excluded, except for genotype, where analyses were run separately for each SNP. For this study we  
26  
27 148 used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs  
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29 149 and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common)  
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31 150 allele.  
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### 36 151 **Statistical methods**

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39 152 First, descriptive statistics were calculated for the cohort and exposure data, and correlations between  
40  
41 153 the total and source-specific exposure estimates for all PM size fractions were determined.  
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44 154 We estimated the association between each PM size fraction for each PM source, with predicted FEV<sub>1</sub>  
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46 155 and FVC, in linear models. First, percent predicted lung function effects associated with PM size  
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48 156 fractions and sources were analysed with exposure as a continuous variable, and estimated for an  
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50 157 interquartile increase in exposure (additionally, the analysis was repeated for lung function in Litres).  
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52 158 Second, we investigated the effects of the highest exposure values by setting high exposure cut-off for  
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54 159 PM above the 90<sup>th</sup> percentile of population exposure, medium exposure at 50-90<sup>th</sup> percentile, with  
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56 160 exposure at or below 50<sup>th</sup> percentile as the reference, and tested these for linear trends. To investigate  
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58 161 clinically significant effects, we modelled increased risk of low lung function with LLN as a cut-off in  
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3 162 logistic models. To assess confounding, covariates were added to regression models one at a time and  
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5 163 were retained in the model if the coefficient of PM was altered by more than 10% by their inclusion.  
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7 164 The covariates included in the final models were age, sex, weight, education, residential area, smoking  
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9 165 status, and exposure to passive smoking in the last 12 months.  
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13 166 For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between  
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15 167 genotypes and lung function for all available SNPs in single-SNP linear models coded as minor allele  
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17 168 dominant effects. We present nominal p-values for these exploratory analyses. To evaluate effect  
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19 169 modification, we tested for interaction of the effects of exposure to different PM size fractions and  
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21 170 sources on lung function by genotype, and report the adjusted means of a fitted model adjusted for  
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23 171 all covariate variables. The significance of the interaction terms was evaluated using a likelihood ratio  
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25 172 tests comparing the model with interaction term to the model without this term.  
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29 173 In sensitivity analysis, the effects of PM were analysed in models stratified by sex, smoking status,  
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31 174 asthma status, atopic status, BMI categories, and age categories to evaluate possible confounding from  
32  
33 175 any of these characteristics.  
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37 176 All regression results for change in lung function were reported as increment or decrement in %  
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39 177 predicted. Change in mL is reported in the supplement. Odds ratios were obtained from the logistic  
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41 178 model analyses. All results are presented as point estimates with 95% confidence intervals, and with  
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43 179 p-values as appropriate. Analyses were performed in R studio.<sup>35</sup>  
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## 46 180 **RESULTS**

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49 181 The ADONIX cohort includes 6685 individuals. After excluding individuals with missing data on  
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51 182 explanatory variables such as smoking status (25), environmental tobacco smoke (76), and who had  
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53 183 missing, or very low quality of lung function (532), there were 6006 individuals, further 333 had a  
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55 184 missing postcode, 315 did not have a European background, and 457 were outside the catchment area  
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58 185 leaving 5216 for the main analysis. In the genetic analysis, up to 276 individuals had missing data.  
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3 186 Finally, 5216 were included with information on the variables related to exposure and health outcomes  
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5 187 used in this study and self-reported European ancestry. The mean age of the study population was  
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7 188 51.6  $\pm$ 11.4 years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and  
8  
9 189 10.2% were exposed to passive smoking. A total of 12.6% (n=656) of the study population had FEV<sub>1</sub>  
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11 below lower limit of normal and 9.5% (n=494) had FVC below LLN. The most common highest  
12 190 education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).  
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17 192 **TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION**

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
<b>Females</b>	2789 (53.5%)
<b>Respiratory health</b>	
FEV <sub>1</sub> (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV <sub>1</sub> , n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV <sub>1</sub> /FVC, n (%)	548 (10.5%)
<b>Smoking</b>	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)
<b>Passive smoking (last 12 months)</b>	534 (10.2%)
<b>Education</b>	

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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.<sup>33</sup> FEV<sub>1</sub>, 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<sup>3</sup> PM<sub>10</sub>, 9.3 µg/m<sup>3</sup> PM<sub>2.5</sub>, and 0.76 µg/m<sup>3</sup> PM<sub>BC</sub> (Table 2). Background long-

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3 195 range transported particle matter constituted the larger proportion of exposure, contributing 75%  
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5 196 and 76% of the total PM<sub>10</sub> and PM<sub>2.5</sub> levels, respectively. The local emission source that contributed  
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7 197 mostly to total PM<sub>10</sub> was traffic, whereas residential heating contributed most to PM<sub>2.5</sub> (Table 2).  
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11 198 **TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY**  
12 199 **POPULATION**

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

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56 200 IQR, interquartile range. SD, standard deviation.

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58 201 Traffic was the largest contributor to PM<sub>BC</sub>, and for PM<sub>BC</sub> the contribution from long-range sources was  
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60 202 considerably lower than for PM<sub>10</sub> and PM<sub>2.5</sub>, at 26%. Traffic sources were originally divided into exhaust



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

### 207 **Effects of PM exposure**

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

212 **TABLE 3 ESTIMATED CHANGE IN FEV<sub>1</sub> AND FVC PER IQR CHANGE IN PM FROM**  
 213 **DIFFERENT SOURCES**

	Delta % predicted FEV <sub>1</sub>				Delta % predicted FVC			
	<i>B</i>	95% CI		p-value	<i>B</i>	95% CI		p-value
		Lower	Upper			Lower	Upper	
<b>PM<sub>10</sub> Total</b>	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	<b>-0.48</b>	<b>-0.89</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.46</b>	<b>-0.83</b>	<b>-0.08</b>	<b>0.02</b>
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
<b>PM<sub>2.5</sub> Total</b>	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	<b>-0.47</b>	<b>-0.88</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.47</b>	<b>-0.83</b>	<b>-0.10</b>	<b>0.01</b>

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3	Residential								
4	heating	-0.30	-0.80	0.20	0.23	-0.03	-0.48	0.43	0.91
5									
6	Marine traffic	0.00	-0.89	0.89	1.00	-0.05	-0.85	0.75	0.66
7									
8	Industry	-0.34	-0.86	0.18	0.21	-0.32	-0.80	0.15	0.18
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14	<b>PM<sub>BC</sub> Total</b>	<b>-0.56</b>	<b>-1.01</b>	<b>-0.12</b>	<b>0.01</b>	<b>-0.53</b>	<b>-0.94</b>	<b>-0.13</b>	<b>0.01</b>
15									
16	Traffic	<b>-0.41</b>	<b>-0.78</b>	<b>-0.03</b>	<b>0.03</b>	<b>-0.43</b>	<b>-0.77</b>	<b>-0.09</b>	<b>0.01</b>
17									
18	Residential								
19	heating	-0.38	-0.89	0.12	0.14	0.00	-0.46	0.45	0.99
20									
21	Marine traffic	-0.01	-0.25	0.23	0.94	-0.05	-0.27	0.16	0.62
22									
23	Industry	-0.40	-0.92	0.12	0.13	-0.38	-0.85	0.09	0.11
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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.

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

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3 224 from traffic were associated with increased odds ratio of having clinically significant reductions in FEV<sub>1</sub>  
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5 225 and FVC (below LLN) (p<0.05; except p=0.08 for FEV<sub>1</sub> and PM<sub>BC</sub>) (Table S4). The ratio FEV<sub>1</sub>/FVC below  
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7 226 LLN was not associated with any exposure (data not shown).  
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### 10 227 **Genetic main effects**

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13 228 All SNPs were in Hardy-Weinberg equilibrium except rs1136450, which has one very rare genotype  
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15 229 (n=12). The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%.  
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17 230 (Table S5). In a main effect analysis without considering environmental exposure, minor allele carrier  
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19 231 status of three GST SNPs was associated with lung function outcomes in minor allele dominant genetic  
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21 232 models. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV<sub>1</sub> reductions  
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23 233 by -0.80% (p=0.044) and -0.90% (p=0.017), respectively, and FVC reductions were seen in minor allele  
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25 234 carriers of the same GSTP1 SNP rs762803 (-0.74%, p=0.042) and the GSTT1 null genotype assessed with  
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27 235 SNP rs2266637 (-1.434%, p=0.001). No main effect associations were found with SP-A SNPs (Table S5).  
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### 32 236 **Effect modification of PM effects**

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35 237 PM<sub>2.5</sub>, which had marginally more consistent effects for traffic-related exposure, was used for  
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37 238 exploratory interaction analyses. The effect of genotype and exposure to PM<sub>2.5</sub> from all sources was  
38  
39 239 analysed in interaction models, and SNPs with exposure-interaction p-values below 0.1 are shown in  
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41 240 Table S6. The number of significant interactions was higher than expected by chance. The most  
42  
43 241 plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure  
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45 242 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV<sub>1</sub>  
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47 243 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result  
48  
49 244 should, however, be seen as highly exploratory. Stratifying data by smoking status, atopy, asthma  
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51 245 status, and BMI category showed no significant effect modification on the estimates for air pollution  
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53 246 effect on lung function in either linear or logistic analysis (data not shown).  
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## 247 DISCUSSION

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

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

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3 271 industrial origin, suggesting that they could be modified by factors related to age, height and sex which  
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5 272 are accounted for in the percent predicted value.  
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8 273 In spite of there being moderate to high correlations (0.75, 0.42 and 0.99) between total PM and traffic  
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10 274 related PM in any of the three fractions (Table S1), total PM<sub>10</sub> and PM<sub>2.5</sub> were not significantly  
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12 275 associated with reductions in percent predicted FVC and FEV<sub>1</sub>. Residential heating is the second largest  
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14 276 local contribution to total PM, and we observed negative correlations between PM from residential  
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16 277 heating and total PM as well as PM from other sources. PM from residential heating could thus be  
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18 278 interpreted as an indicator of low exposure to other sources of air pollution which might contribute to  
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20 279 explaining the few suggested inverse (positive) associations seen in some categorical analyses between  
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22 280 PM from residential heating and FEV<sub>1</sub> and FVC (e.g. Figure 1).  
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27 281 For GSTP and GSTT genotypes, where carrying the minor or null allele, were associated with decreased  
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29 282 percent predicted FEV<sub>1</sub> and FVC, whereas no direct effects of SP-ASNPS were found (Table S4). Gene-  
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31 283 environment interactions were tested for all SNPs and all PM sources and size fraction, but significant  
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33 284 and biologically plausible interactions were only observed between specific SP-A SNPs and exposure  
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35 285 to PM<sub>2.5</sub> from marine traffic and industrial sources, and not for traffic or total PM, where most direct  
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37 286 effects were observed. We thus infer that it is possible that detrimental effects from marine traffic  
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39 287 and industry PM t may affect specific individuals with genetic susceptibilities.<sup>14</sup> Industrial exposure in  
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41 288 Gothenburg is concentrated along the northern mouth of the Göta Älv River and is dominated by a  
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43 289 power plant and oil refineries. PM from marine traffic is also concentrated along the river.  
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48 290 During initial analysis and covariate selection, we found that residential region was an effect modifier,  
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50 291 and included this as a covariate in the study. Other studies of lung function within a single region have  
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52 292 adjusted for municipality to avoid confounding of the results which is likely due socio-economic  
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54 293 distribution of the study population in some urban areas, where high-exposed areas also have a high  
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56 294 proportion of individuals with high socio-economic status which entails other risk factor panorama and  
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58 295 health behaviours.<sup>37</sup>  
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3 296 In a previous study on the same cohort population, short distance to the nearest road was found to be  
4  
5 297 associated with decreases in FEV<sub>1</sub> and FVC.<sup>38</sup> Comparing with other studies, the size of the estimated  
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7 298 change in lung function in our study are similar and within confidence intervals of those reported from  
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10 299 the UK biobank.<sup>3</sup> The pollution levels found in the current study were moderate compared to those  
11  
12 300 presented in the study from Adam and colleagues, reporting significant associations for both FEV<sub>1</sub> and  
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14 301 FVC in adults related to long term exposure to NO<sub>2</sub>, NO<sub>x</sub> and PM<sub>10</sub>, but not PM<sub>2.5</sub> or coarse PM in a  
15  
16 302 meta-analysis of the ESCAPE data.<sup>7</sup> In our study, both of NO<sub>x</sub> and NO<sub>2</sub> were highly correlated with  
17  
18 303 traffic PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (all correlations  $r > 0.79$ ), for the years that both NO<sub>x</sub> and NO<sub>2</sub> and source  
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20  
21 304 specific PM estimates were available.

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24 305 Effects specifically of exposure to industrial emissions have not been widely studied, and industry  
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26 306 emissions are often pooled with other sources,<sup>29</sup> or considered negligible as high stacks disperse the  
27  
28 307 emissions.<sup>39</sup> Studies of respiratory health with source specific results generally find associations mainly  
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30 308 with traffic: In the study of Jacquemin and colleagues,<sup>8</sup> only traffic, and not industry-specific particles  
31  
32 309 were associated with the lung damage marker CC16. Krall and colleagues<sup>13</sup> observed only effects from  
33  
34 310 tailpipe exhaust on lung function and eNO. Billet and colleagues<sup>9</sup> exposed cells *in-vitro* to particles from  
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36 311 a highly industrialized environment and found that ultrafine particles with higher concentrations of  
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38 312 polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response.  
39  
40 313 Peng and colleagues<sup>6</sup> observed that PM from vehicle emissions, diesel engines and wood burning were  
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42 314 associated with the largest increases in emergency hospital admissions for CVD and respiratory  
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44 315 disease.<sup>6</sup> In a multi-city European study<sup>40</sup> there were negative associations between FEV<sub>1</sub> and PM from  
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46 316 nickel and sulphur, however results were not consistent between cities, perhaps reflecting the  
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50 317 heterogeneity in particle compositions in different cities in the study.<sup>41</sup>

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54 318 SP-A has the ability to bind and help clear pathogens but also particle matter from the lungs by  
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56 319 opsonisation<sup>22</sup> and is activated in response to exposure to Ozone, another major air pollutant<sup>42</sup>  
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58 320 Previous literature suggest that SNPs of SP-A are associated with defect opsonisation, and hence  
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3 321 increased risk for viral infections,<sup>43</sup> but likely also for adverse effects of particle exposure (as well as  
4  
5 322 volatile exposures.<sup>22</sup> We found a significant interaction between polymorphisms of two SP-A1 SNPs  
6  
7 323 and the association between exposure to PM from industrial sources and lung function. Other studies  
8  
9  
10 324 have found rs1059057 to be associated with acute lung injury<sup>22</sup> and cystic fibrosis,<sup>44</sup> and rs1136451  
11  
12 325 with susceptibility to COPD and analysed gene-environment effects from tobacco smoking.<sup>24</sup> The SP-A  
13  
14 326 2 SNP rs4253527 has been associated with tuberculosis.<sup>22</sup>

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16  
17 327 We observed no gene-environment interactions with any GSTT or GSTP SNPs. The GSTP SNP rs1695  
18  
19 328 has been associated with possible increased asthma risk of air pollution exposure,<sup>19</sup> whereas we found  
20  
21 329 a main effect with lower FEV<sub>1</sub> in the current study of adults, but no interactions. These genetic  
22  
23 330 interactions results should be seen as exploratory and be interpreted with caution.

### 24 25 26 27 331 **Strengths and limitations**

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29 332 The cohort data used in this study were collected to study respiratory health, and provides a rich  
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31 333 dataset containing a large number of variables of interest. In the model selection, adding additional  
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33 334 covariates as potential confounders did not affect the regression estimates substantially.  
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35 335 Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered  
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37 336 2001–2003) and showed that women, the elderly, and individuals with university education were more  
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39 337 likely to participate.<sup>28</sup> As we adjusted for these covariates and as exposure was unknown to  
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41 338 participants, this is not likely to bias the current results.

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45 339 The number of individuals who fell below the lower limit of normal for both FEV<sub>1</sub> and FVC was rather  
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47 340 high, as this value is defined as the 5<sup>th</sup> percentile in a healthy, non-smoking population. It is possible  
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49 341 that individuals with respiratory issues, as well as past and present smokers, are more likely to take  
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51 342 part in a study such as ADONIX.<sup>28</sup> On the other hand, with clinical outcome measures and an exposure  
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53 343 which was not known to the participants, this is an unlikely source of important bias.

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57 344 In this study, complete residential histories, including duration of residence, were not available.  
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59 345 Instead, we used a single modelled value for residential exposure that was matched by year of  
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3 346 participation for each individual, rather than a complete longitudinal exposure history over multiple  
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5 347 years. We consider this a reasonable approach, as the between-year correlation in air pollution  
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7 348 concentrations and emissions in a certain location is very high.

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10 349 As people spend a fair proportion of their time outside their home, and our results are based on  
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12 350 modelled air pollution data at the place of residence, the exposure represents an approximation of the  
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14 351 real exposure. However, this is an established method which provides a fair picture of the actual  
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16 352 exposure. The resulting, and likely nondifferential, misclassification of exposure would, however, then  
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18 353 to shrink risk estimates towards the null. The model was developed using new emissions inventories,  
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20 354 updated information on vehicle composition, and had been further verified by measurements.<sup>29</sup>  
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22 355 However, for residential heating, the source assignment is based on proxies such as building type, as  
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24 356 no actual source inventory was available, and may have a poorer performance.

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29 357 The very high correlations between traffic-related PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (Table S1) mean that it is  
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31 358 difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to  
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33 359 high correlations between the various PM source measures also meant we had to refrain from using  
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35 360 multi-pollutant models, meaning that the estimates associated with each exposure type must be  
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37 361 interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent  
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39 362 associations with FEV<sub>1</sub> and FVC, whereas the other source-specific exposures did not.

## 40 41 42 43 363 **CONCLUSION**

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46 364 In this large study of clinically measured outcomes in a general population sample we found that  
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48 365 exposure to traffic particles of all three studied PM species and size fractions were associated with  
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50 366 reductions in FEV<sub>1</sub> and FVC and increased risk of low FEV<sub>1</sub> and FVC (below LLN), supporting the need  
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52 367 for measures to reduce urban pollution from traffic to protect urban populations. Furthermore, we  
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54 368 found intriguing suggestions in our exploratory analysis that the SP-A1 gene may play a part in  
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56 369 susceptibility to air pollution from industrial sources, possibly due to its very different composition.  
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3 370 **Author Contributions**  
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5 371 HKC analysed the data and drafted the manuscript. FN, KT, and A-CO provided the cohort  
6 372 and genetic data, contributed to essential parts of the introduction and discussion and the final  
7 373 manuscript. DS provided and documented the PM exposure data. All authors approved the  
8 374 final version of the manuscript and contributed to the discussion.  
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12 375 **Data statement**  
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14  
15 376 Additional data from the ADONIX study exist and are held by the authors.  
16

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19  
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21 379 Council Formas, The Swedish Society for Medical Research and the Swedish Environmental  
22 380 Protection Agency.  
23  
24

25 381 **Competing interests**  
26

27 382 None declared.  
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30 383 Ethics approval: The Västra Götaland Region ethical review board approved of the study (ref  
31 384 no. Ö 092-01) and participants gave informed consent.  
32  
33

34 385 **Legends**  
35

36 386 Figure 1 Change in FEV<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50<sup>th</sup> to  
37 387 90<sup>th</sup>) and high (above 90<sup>th</sup> percentile) concentration of source-specific PM  
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43 389 Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV<sub>1</sub> and  
44 390 FVC in exposure categories to select PM sources. Dotted lines represent effects on minor  
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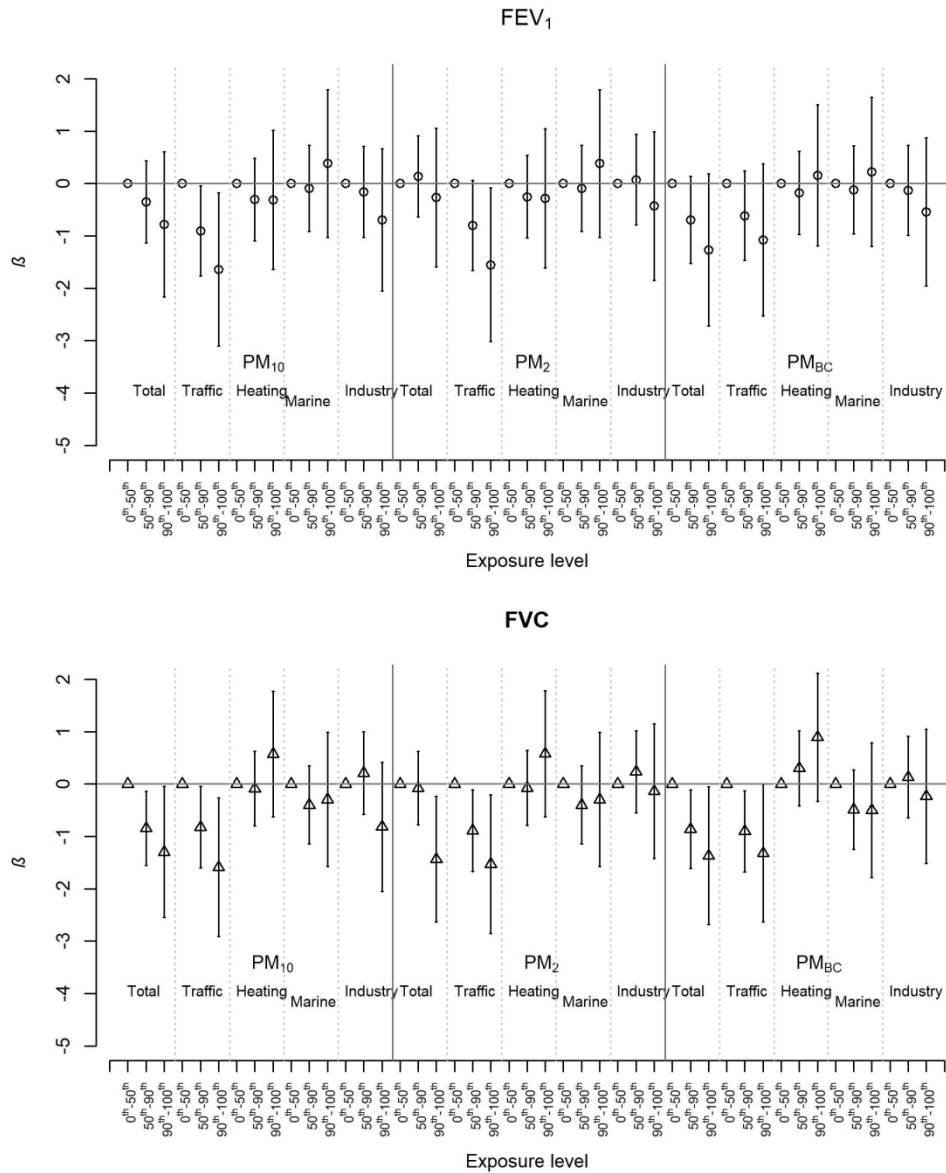


Figure 1 Change in FEV<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

169x203mm (300 x 300 DPI)

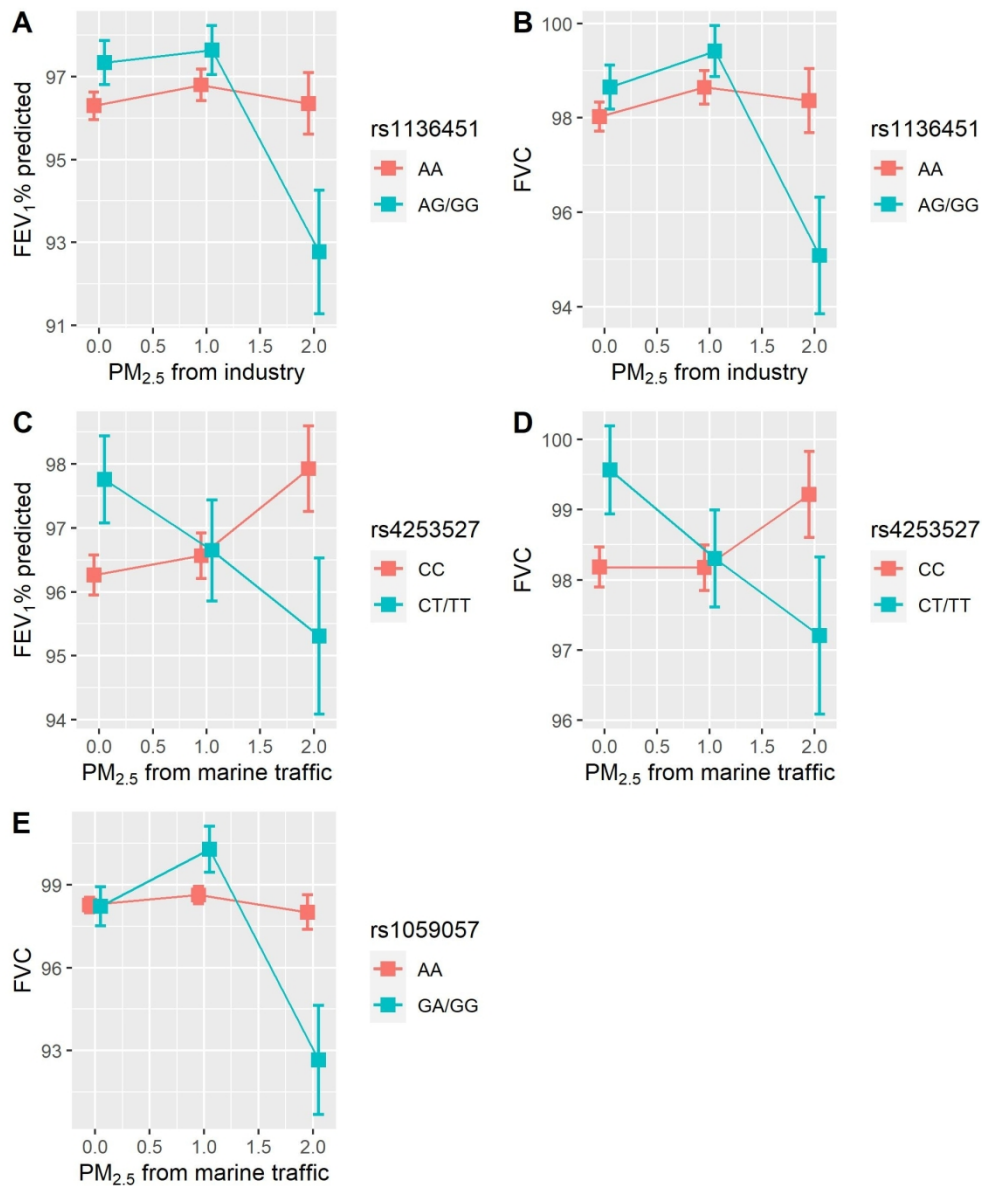


Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV<sub>1</sub> and FVC in exposure categories to select PM sources with standard error bars. Dotted lines represent effects on minor allele carriers

169x203mm (300 x 300 DPI)

Supplementary tables for ADONIX: Lung function and source specific PM

Table S1 Correlation (Pearson's) matrix of exposure

		PM <sub>10</sub>					PM <sub>2.5</sub>					PM <sub>BC</sub>				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM <sub>10</sub>	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 <sub>2.5</sub>	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 <sub>BC</sub>	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

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Supplementary tables for ADONIX: Lung function and source specific PM

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

	FEV <sub>1</sub>				FVC			
	$\beta$	95% CI		$p$	$\beta$	95% CI		$p$
		Lower	Upper			Lower	Upper	
<b>PM<sub>10</sub></b>								
Total	-0.37	-0,97	0,22	0.22	<b>-0.73</b>	-1,27	-0,19	<b>0.01</b>
Traffic	<b>-0.85</b>	-1,51	-0,19	<b>0.01</b>	<b>-0.81</b>	-1,40	-0,21	<b>0.01</b>
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
<b>PM<sub>2.5</sub></b>								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	<b>-0.79</b>	-1,45	-0,13	<b>0.02</b>	<b>-0.81</b>	-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
<b>PM<sub>BC</sub></b>								
Total	<b>-0.66</b>	-1,30	-0,01	<b>0.05</b>	-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<sub>1</sub> and FVC (mL) per IQR change in PM exposure**

	IQR ( $\mu\text{g}/\text{m}^3$ )	FEV <sub>1</sub>			FVC		
		$\beta$	95% CI		$\beta$	95% CI	
			Lower	Upper		Lower	Upper
<b>PM<sub>10</sub></b>							
Total	3.05	-23	-46	0	-11	-30	8
Traffic	1.64	<b>-23</b>	<b>-43</b>	<b>-4</b>	<b>-20</b>	<b>-36</b>	<b>-4</b>
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-8	16	4	-6	13
Industry	0.10	<b>-26</b>	<b>-47</b>	<b>-5</b>	<b>-18</b>	<b>-35</b>	<b>-1</b>
<b>PM<sub>2.5</sub></b>							
Total	2.47	<b>-28</b>	<b>-54</b>	<b>-3</b>	-5	-26	15
Traffic	0.52	<b>-24</b>	<b>-43</b>	<b>-5</b>	<b>-20</b>	<b>-36</b>	<b>-4</b>
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-38	46	4	-30	38
Industry	0.06	<b>-24</b>	<b>-49</b>	<b>0</b>	<b>-18</b>	<b>-38</b>	<b>2</b>
<b>PM<sub>BC</sub></b>							
Total	0.33	<b>-29</b>	<b>-50</b>	<b>-8</b>	<b>-25</b>	<b>-42</b>	<b>-7</b>
Traffic	0.25	<b>-24</b>	<b>-42</b>	<b>-6</b>	<b>-18</b>	<b>-33</b>	<b>-4</b>
Residential heating	0.07	4	-21	28	-11	-31	8
Marine traffic	0.01	3	-8	15	3	-6	13
Industry	0.01	<b>-27</b>	<b>-51</b>	<b>-2</b>	<b>-20</b>	<b>-40</b>	<b>0</b>

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<sub>1</sub> and FVC below LLN in medium and high exposure strata by PM source and size fraction\***

Model	Percentile	LLN FEV <sub>1</sub>				LLN FVC			
		OR	95% CI		p	OR	95% CI		p
			lower	upper			lower	upper	
<b>PM<sub>10</sub></b>									
Total	0-50 <sup>th</sup>	-	-	-	-				
	50 <sup>th</sup> -90 <sup>th</sup>	1.05	0.87	1.26	0.61	<b>1.23</b>	<b>1.00</b>	<b>1.51</b>	<b>0.05</b>
	90 <sup>th</sup> -100 <sup>th</sup>	1.18	0.86	1.62	0.31	<b>1.40</b>	<b>0.98</b>	<b>1.99</b>	<b>0.06</b>
Traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.46</b>	<b>1.06</b>	<b>2.02</b>	<b>0.02</b>	<b>1.45</b>	<b>1.00</b>	<b>2.08</b>	<b>0.05</b>
Residential heating	0-50 <sup>th</sup>	ref	-	-	-		ref	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79
	90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49
<b>PM<sub>2.5</sub></b>									
Total	0-50 <sup>th</sup>								
	50 <sup>th</sup> -90 <sup>th</sup>	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77
	90 <sup>th</sup> -100 <sup>th</sup>	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11
Traffic	0-50 <sup>th</sup>	ref	-	-	-				
	50 <sup>th</sup> -90 <sup>th</sup>	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.47</b>	<b>1.06</b>	<b>2.03</b>	<b>0.02</b>	<b>1.54</b>	<b>1.07</b>	<b>2.21</b>	<b>0.02</b>
Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	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

1		90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
2	<b>PM<sub>BC</sub></b>									
3		Total					ref	-	-	
4		0-50 <sup>th</sup>								
5		50 <sup>th</sup> -90 <sup>th</sup>	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
6		90 <sup>th</sup> -100 <sup>th</sup>	1.34	0.97	1.86	0.08	<b>1.46</b>	<b>1.02</b>	<b>2.09</b>	<b>0.04</b>
7	Traffic	0-50 <sup>th</sup>	ref	-	-	-				
8		50 <sup>th</sup> -90 <sup>th</sup>	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
9		90 <sup>th</sup> -100 <sup>th</sup>	1.37	0.98	1.90	0.06	<b>1.55</b>	<b>1.08</b>	<b>2.23</b>	<b>0.02</b>
10	Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
11		50 <sup>th</sup> -90 <sup>th</sup>	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
12		90 <sup>th</sup> -100 <sup>th</sup>	0.80	0.57	1.11	0.18	<b>0.64</b>	<b>0.44</b>	<b>0.94</b>	<b>0.02</b>
13	Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
14		50 <sup>th</sup> -90 <sup>th</sup>	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
15		90 <sup>th</sup> -100 <sup>th</sup>	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
16	Industry	0-50 <sup>th</sup>					ref	-	-	
17		50 <sup>th</sup> -90 <sup>th</sup>	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
18		90 <sup>th</sup> -100 <sup>th</sup>	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<sub>1</sub>, 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.

Supplementary tables for ADONIX: Lung function and source specific PM

**Table S5 Genetic main effects: Changes in FEV<sub>1</sub> and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs**

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

## Supplementary tables for ADONIX: Lung function and source specific PM

1											
2		(TT+TC)	848 (18.5)								
3		vs CC	3735 (81.5)	0.479	-0.513	1.471	0.344	0.508	-0.392	1.408	0.269
4	<b>SP-A 2</b>										
5		rs1059046									
6		(GG+GT)	2814 (61.8)								
7		vs TT	1741 (38.2)	0.070	-0.724	0.865	0.862	0.038	-0.682	0.759	0.917
8		rs1965707									
9		(AA+AG)	2103 (46.2)								
10		vs GG	2449 (53.8)	0.085	-0.686	0.856	0.829	0.255	-0.446	0.956	0.476
11		rs1965708 )									
12		(TT+TG)	1551 (33.8)								
13		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.

Supplementary tables for ADONIX: Lung function and source specific PM

**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
<b>FEV<sub>1</sub></b>						
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	<b>rs1136450</b>	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	<b>0.04</b>	<b>0.01</b>
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	<b>0.02</b>	P>0.1
SP-A2	<b>rs1059046</b>	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
<b>FVC</b>						
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	<b>0.03</b>
GSTT1	rs2266637	0.048	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	<b>rs1136450</b>	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	<b>0.01</b>
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	<b>0.03</b>	P>0.1
SP-A2	<b>rs1059046</b>	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	<b>0.03</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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.
<b>Results</b>			
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.
<b>Discussion</b>			
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
<b>Other information</b>			
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.

1 \*Give information separately for exposed and unexposed groups.  
2  
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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
5 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
6 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
7 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
8 available at <http://www.strobe-statement.org>.  
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# BMJ Open

## 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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Keywords:	EPIDEMIOLOGY, GENETICS, PARTICLE MATTER, SURFACTANT PROTEIN A, glutathione S-transferase, LUNG FUNCTION

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Lung function and PM species data from SCAC

**1 Title page**

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

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18 **Word count: 3506**

**19 Keywords:**

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

1  
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3 21 **ABSTRACT**  
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5

6 22 **objectives:** To investigate the long-term effects of source-specific particle matter (PM) on lung  
7  
8 23 function, effects of Surfactant Protein A (SP-A) and glutathione S-transferase (GST) genes GSTP1  
9  
10 24 and GSTT1 gene variants and effect modification by single nucleotide polymorphism (SNP)  
11  
12 25 genotype.  
13  
14

15 26 **design:** Cohort study with address-based annual PM exposure assigned from annual estimates of  
16  
17 27 size (PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub>) and source-specific (traffic, industry, marine traffic and wood burning)  
18  
19 28 dispersion modelling.  
20  
21

22 29 **setting:** Gothenburg, Sweden.  
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24

25 30 **participants:** The ADONIX study had 6685 participants recruited from the general population,  
26  
27 31 of which 5216 (78%) were included in the current study with information on all variables of  
28  
29 32 interest. Mean age at the time of enrolment was 51.4 years (range 24-76) and 2427 (46.5%)  
30  
31 33 were males.  
32  
33

34 34 **primary and secondary outcome measures:** The primary outcome was forced vital capacity  
35  
36 35 (FVC) and forced expiratory flow in 1 second (FEV<sub>1</sub>). Secondary outcome measure were effects  
37  
38 36 and gene-environment interactions of SP-A and GSTT1 and GSTP1 genotypes.  
39  
40

41 37 **results:** Exposure to traffic-related PM<sub>10</sub> and PM<sub>2.5</sub> was associated with decreases in percent-  
42  
43 38 predicted FEV<sub>1</sub> by -0.48% (95%CI -0.89% to -0.07%) and -0.47% (95%CI -0.88% to -0.07%)  
44  
45 39 per interquartile range (IQR) 3.05 and 2.47 µg/m<sup>3</sup>, respectively, and with decreases in percent-  
46  
47 40 predicted FVC by -0.46% (95%CI -0.83% to -0.08%) and -0.47% (95%CI -0.83% to -0.10%).  
48  
49 41 Total and traffic-related PM<sub>BC</sub> was strongly associated with both FEV<sub>1</sub> and FVC by -0.53  
50  
51 42 (95%CI -0.94 to -0.13%) and -0.43% (95%CI -0.77 to -0.09%) per IQR, respectively, for FVC,  
52  
53 43 and similarly for FEV<sub>1</sub>. Minor allele carrier status for two GSTP1 SNPs and the GSTT1 null  
54  
55 44 genotype were associated with decreases in percent-predicted lung function. Three SP-A SNPs  
56  
57 45 showed effect modification with exposure to PM<sub>2.5</sub> from industry and marine traffic.  
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6 47 **conclusions:** PM exposure, specifically traffic-related, was associated with FVC and FEV<sub>1</sub>  
7  
8 48 reductions and not modified by genotype. Genetic effect modification was suggested for industry  
9  
10 49 and marine traffic PM<sub>2.5</sub>.

11  
12  
13 50 **Article summary:** Strength and limitations of this study  
14

- 15  
16 51 • An extensive dispersion model of source-specific PM was assigned to a large, general  
17  
18 52 population cohort of adults in a single urban region  
19  
20 53 • The cohort was designed with focus on respiratory health and a broad range of covariates  
21  
22 54 were collected as well as genotyping for genes with known associations with respiratory  
23  
24 55 health  
25  
26 56 • Spirometry was performed according to a standardized maneuver by trained personnel  
27  
28 57 although not with reversibility test  
29  
30 58 • A full residential history was not available and thus exposure was assigned for the time of the  
31  
32 59 participation and indoor or occupational air pollution exposure was not taken into account.”  
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## 60 INTRODUCTION

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

71 In epidemiological studies, air pollution is most often assigned to certain sources by building exposure  
72 profiles from particle size distributions and relative concentrations of specific chemicals in the  
73 particles. Traffic pollution is for example characterized by NO<sub>x</sub> and ultrafine particles.<sup>7</sup> Particles from  
74 petrochemical industries are characterized by trace elements such as nickel, cobalt, caesium and  
75 lanthanum,<sup>10</sup> and particles from other industry is characterized by high levels of trace metals vanadium  
76 and nickel,<sup>10 11</sup> but are of course sector-dependent. Similarly, PM from marine traffic is subject to large  
77 uncertainties as fuel types and fleet types vary across the world.<sup>12</sup> However, this field of research is  
78 expanding rapidly as exposure science evolves with more sophisticated source specific models.<sup>13</sup>  
79 Beyond the importance of exposure composition and source, individual susceptibility to air pollution  
80 is modified by many factors, including genetic differences. Susceptibility related to genetic variability  
81 may improve our understanding of the physiological mechanisms underlying health effects of air  
82 pollution.<sup>14 15</sup> Glutathione S-transferase (GST) are involved in metabolizing reactive oxygen species to  
83 reduce oxidative stress.<sup>16</sup> GSTP1 SNPs have been reported to modify the risk of cardiovascular disease  
84 associated with exposure to NO<sub>2</sub><sup>17</sup> and to modify the association between NO<sub>2</sub> and lung function



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3 85 decline in adults,<sup>18</sup> but findings are inconsistent and no meta-analysis has been performed.<sup>19,20</sup>  
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5 86 Surfactant protein A (SP-A) is found in the surfactant fluid which lines the lung alveoli and has  
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7 87 important functions in the innate immune system of the lungs, especially for opsonizing inhaled  
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9  
10 88 material.<sup>21</sup> SP-A gene polymorphisms are associated with development of serious pulmonary disease  
11  
12 89 and are involved in the pulmonary defence against pathogens.<sup>22</sup> SNPs in SP-A coding regions have been  
13  
14 90 associated with multiple respiratory diseases,<sup>14 23</sup> as well as gene-environment interactions for  
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16 91 smoking and chronic obstructive pulmonary disease.<sup>24</sup>  
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19 92 Many questions remain as to what components of air pollution are harmful in a general population, in  
20  
21 93 particular at relatively low pollution exposures, and if such associations are modified by genetic factors.  
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23 94 Thus, the aim of the current study was to investigate the effects of different PM sources determined  
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25 95 from a state-of the arts dispersion model on lung function in a general population cohort, and to  
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27 96 investigate lung function effects of genotype and gene-environment interaction with particle  
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29 97 exposures types.  
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## 33 98 **METHODS**

### 34 99 **Study population**

35  
36  
37 100 The study population originates from the ADONIX (ADult-Onset asthma and Nitric oxide) cohort, a  
38  
39 101 random sample of subjects aged 24-76 years who were invited to participate in a clinical examination  
40  
41 102 between 2001-2008, as previously described.<sup>17 25-28</sup> In brief, the overall participation rate was 46%, all  
42  
43 103 participants provided data on residential address, lifestyle factors and education, presence of allergic  
44  
45 104 airway inflammation and respiratory health, as well as clinical measurements of lung function, such as  
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47 105 spirometry (single manoeuvre) and nitric oxide in exhaled air (FENO). Blood samples were collected  
48  
49 106 for DNA extraction and subsequently genotyped for selected SNPs from the SP-A, GSTP1, and GSTT1  
50  
51 107 genes.  
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### 58 108 **Exposure assessment**

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3 109 As a part of the involvement in the Swedish Clean Air and Climate project (SCAC), the Swedish  
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5 110 Meteorological and Hydrological Institute (SMHI) modelled source-specific, annual particulate matter  
6  
7 111 (PM) concentrations for different size fractions for each calendar year in the period 1990 to 2011 using  
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9 112 dispersion modelling described in detail by Segersson and colleagues, 2017, including a detailed map  
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11 113 of the area.<sup>29</sup> PM<sub>10</sub> and PM<sub>2.5</sub> represent particles smaller than 10 and 2.5 micrometers (µm)  
12  
13 114 respectively, whereas black carbon particles, PM<sub>BC</sub>, are soot particles from combustion, notably vehicle  
14  
15 115 exhaust. The specific sources that were investigated were traffic (exhaust and road wear for PM<sub>10</sub> and  
16  
17 116 PM<sub>2.5</sub>, exhaust only for PM<sub>BC</sub>), residential heating (predominantly house heating using wood assessed  
18  
19 117 as area sources), marine traffic (averaged description from a bottom-up calculation using actual  
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21 118 positions of ships in port, manoeuvring and cruising), and industrial sources (point sources, in  
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23 119 Gothenburg dominated by refineries, energy plants, and other industry).<sup>30</sup> Background concentration  
24  
25 120 (long-range transport particles), was also provided, but was estimated indirectly as the difference  
26  
27 121 between total modelled local contribution and monitoring data from a central urban background  
28  
29 122 station. Consequently, it showed no spatial variation and was not used for analyses. To refine the  
30  
31 123 estimated contribution of traffic, an increment due to reduced ventilation in street canyons was added  
32  
33 124 for the busiest streets. The increment was estimated as the difference between simulations with and  
34  
35 125 without buildings using the OSPM model.<sup>31</sup> For each study participant's residential address at the date  
36  
37 126 of clinical examination, annual mean values of pollutants were calculated separately for the five source  
38  
39 127 categories and modelled exposure grid values of all PM fractions were matched to the year of the  
40  
41 128 participant's clinical examination.

### 129 **Outcome definitions**

50  
51 130 Dynamic spirometry including FEV<sub>1</sub> and FVC was performed with the subject in a sitting position using  
52  
53 131 a nose clip without bronchodilation. In all measurements, a Jaeger Master Screen PFT (Vyair,  
54  
55 132 Mettawa, IL, US) was used. All procedures were performed according to ATS/ERS standards.<sup>32</sup> A local  
56  
57 133 reference material was used for calculation of percent predicted (% predicted) of FEV<sub>1</sub> and FVC and  
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3 134 lower limit of normal, (LLN, the lower 5<sup>th</sup> percentile in healthy individuals) for FEV<sub>1</sub> and FVC.<sup>33 34</sup> Asthma  
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5 135 was defined as reporting having had at least one asthma attack in the previous 12 months, and atopy  
6  
7 136 was defined as having a positive phadiatop test. We used FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC below LLN as an  
8  
9 137 indicator of clinically significant lung function reductions or air flow limitation.  
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13 138 Based on questionnaire replies, smoking status was categorised into current, former (no smoking  
14  
15 139 during the last year) and never smoking. Upon inspection of the distribution of total and traffic particles  
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17 140 within residential regions, postcodes were categorised into four residential areas: Inner city, non-  
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19 141 central city, suburban, and outer suburb or rural. Education was categorised in six categories:  
20  
21 142 elementary school, lower secondary school, training or girls' school, grammar school, university, and  
22  
23 143 "other" or not reported. Individuals who did not have information on all variables of interest were  
24  
25 144 excluded, except for genotype, where analyses were run separately for each SNP. For this study we  
26  
27 145 used genotype data on four GSTP1 SNPs, a SNP marker for the GSTT1 null genotype, four SP-A1 SNPs  
28  
29 146 and three SP-A2 SNPs. All SNPs were coded using a dominant model for the minor (least common)  
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31 147 allele.  
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## 36 148 **Statistical methods**

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39 149 First, descriptive statistics were calculated for the cohort and exposure data, and correlations between  
40  
41 150 the total and source-specific exposure estimates for all PM size fractions were determined.  
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44 151 We estimated the association between each PM size fraction for each PM source, with predicted FEV<sub>1</sub>  
45  
46 152 and FVC, in linear models. First, percent predicted lung function effects associated with PM size  
47  
48 153 fractions and sources were analysed with exposure as a continuous variable, and estimated for an  
49  
50 154 interquartile increase in exposure (additionally, the analysis was repeated for lung function in Litres).  
51  
52 155 Second, we investigated the effects of the highest exposure values by setting high exposure cut-off for  
53  
54 156 PM above the 90<sup>th</sup> percentile of population exposure, medium exposure at 50-90<sup>th</sup> percentile, with  
55  
56 157 exposure at or below 50<sup>th</sup> percentile as the reference, and tested these for linear trends. To investigate  
57  
58 158 clinically significant effects, we modelled increased risk of low lung function with LLN as a cut-off in  
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3 159 logistic models. To assess confounding, covariates were added to regression models one at a time and  
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5 160 were retained in the model if the coefficient of PM was altered by more than 10% by their inclusion.  
6  
7 161 The covariates included in the final models were age, sex, weight, education, residential area, smoking  
8  
9 162 status, and exposure to passive smoking in the last 12 months.  
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13 163 For genetic markers, we assessed Hardy-Weinberg equilibrium, then analysed the association between  
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15 164 genotypes and lung function for all available SNPs in single-SNP linear models coded as minor allele  
16  
17 165 dominant effects. We present nominal p-values for these exploratory analyses. To evaluate effect  
18  
19 166 modification, we tested for interaction of the effects of exposure to different PM size fractions and  
20  
21 167 sources on lung function by genotype, and report the adjusted means of a fitted model adjusted for  
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23 168 all covariate variables. The significance of the interaction terms was evaluated using a likelihood ratio  
24  
25 169 tests comparing the model with interaction term to the model without this term.  
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29 170 In sensitivity analysis, the effects of PM were analysed in models stratified by sex, smoking status,  
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31 171 asthma status, atopic status, BMI categories, and age categories to evaluate possible confounding from  
32  
33 172 any of these characteristics.  
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37 173 All regression results for change in lung function were reported as increment or decrement in %  
38  
39 174 predicted. Change in mL is reported in the supplement. Odds ratios were obtained from the logistic  
40  
41 175 model analyses. All results are presented as point estimates with 95% confidence intervals, and with  
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43 176 p-values as appropriate. Analyses were performed in R studio.<sup>35</sup>  
44  
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## 46 177 **Patient and public involvement**

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49 178 Patients and the public were not involved in the design, or conduct, or reporting of the present  
50  
51 179 research.  
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## 54 180 **RESULTS**

55  
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57 181 The ADONIX cohort includes 6685 individuals. After excluding individuals with missing data on  
58  
59 182 explanatory variables such as smoking status (25), environmental tobacco smoke (76), and who had  
60

183 missing, or very low quality of lung function (532), there were 6006 individuals, further 333 had a  
 184 missing postcode, 315 did not have a European background, and 457 were outside the catchment area  
 185 leaving 5216 for the main analysis. In the genetic analysis, up to 276 individuals had missing data.  
 186 Finally, 5216 were included with information on the variables related to exposure and health outcomes  
 187 used in this study and self-reported European ancestry. The mean age of the study population was  
 188  $51.6 \pm 11.4$  years and 46.5% were males, 46.1% had never smoked, 16.5% were current smokers and  
 189 10.2% were exposed to passive smoking. A total of 12.6% (n=656) of the study population had FEV<sub>1</sub>  
 190 below lower limit of normal and 9.5% (n=494) had FVC below LLN. The most common highest  
 191 education level was university education (37.1%), followed by grammar school (23.0%) (Table 1).

192 **TABLE 1 CHARACTERISTICS OF THE STUDY POPULATION**

N=5216	
Age, mean (SD)	51.6 (11.4)
Males, n (%)	2427 (46.5%)
<b>Females</b>	2789 (53.5%)
<b>Respiratory health</b>	
FEV <sub>1</sub> (% of predicted*), mean (SD)	96.6 (13.7)
FVC (% of predicted*), mean (SD)	97.9 (12.4)
Below LLN of predicted FEV <sub>1</sub> , n (%)	656 (12.6%)
Below LLN of predicted FVC, n (%)	494 (9.5%)
Below LLN of FEV <sub>1</sub> /FVC, n (%)	548 (10.5%)
<b>Smoking</b>	
Current smokers, n (%)	860 (16.5%)
Former smokers, n (%)	1951 (37.4%)
Never smokers, n (%)	2405 (46.1%)

<b>Passive smoking (last 12 months)</b>	534 (10.2%)
<b>Education</b>	
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%)
<b>Residential area</b>	
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%)
<b>Self-reported respiratory health**</b>	
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)

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FEV<sub>1</sub>, 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.<sup>33</sup>

\*\*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)

193 The mean annual air pollution levels at the residential addresses in the study population at study entry  
 194 were moderate, at 15.7  $\mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ , 9.3  $\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ , and 0.76  $\mu\text{g}/\text{m}^3$   $\text{PM}_{\text{BC}}$  (Table 2). Background long-  
 195 range transported particle matter constituted the larger proportion of exposure, contributing 75%  
 196 and 76% of the total  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  levels, respectively. The local emission source that contributed  
 197 mostly to total  $\text{PM}_{10}$  was traffic, whereas residential heating contributed most to  $\text{PM}_{2.5}$  (Table 2).

198 **TABLE 2 DESCRIPTIVE STATISTICS OF EXPOSURE PARAMETERS IN THE STUDY**  
 199 **POPULATION**

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

200 IQR, interquartile range. SD, standard deviation.

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

### 207 Effects of PM exposure

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

212 **TABLE 3 ESTIMATED CHANGE IN  $FEV_1$  AND FVC PER IQR CHANGE IN PM FROM**  
 213 **DIFFERENT SOURCES**

	Delta % predicted $FEV_1$				Delta % predicted FVC			
	<i>B</i>	95% CI		p-value	<i>B</i>	95% CI		p-value
		Lower	Upper			Lower	Upper	
<b><math>PM_{10}</math> Total</b>	-0.16	-0.64	0.33	0.53	-0.37	-0.81	0.07	0.10
Traffic	<b>-0.48</b>	<b>-0.89</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.46</b>	<b>-0.83</b>	<b>-0.08</b>	<b>0.02</b>
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



<b>PM<sub>2.5</sub> Total</b>	0.00	-0.53	0.53	1.00	-0.47	-0.95	0.01	0.05
Traffic	<b>-0.47</b>	<b>-0.88</b>	<b>-0.07</b>	<b>0.02</b>	<b>-0.47</b>	<b>-0.83</b>	<b>-0.10</b>	<b>0.01</b>
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
<b>PM<sub>BC</sub> Total</b>	<b>-0.56</b>	<b>-1.01</b>	<b>-0.12</b>	<b>0.01</b>	<b>-0.53</b>	<b>-0.94</b>	<b>-0.13</b>	<b>0.01</b>
Traffic	<b>-0.41</b>	<b>-0.78</b>	<b>-0.03</b>	<b>0.03</b>	<b>-0.43</b>	<b>-0.77</b>	<b>-0.09</b>	<b>0.01</b>
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.

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

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3 221 of FEV<sub>1</sub> and FVC associated with PM<sub>10</sub> traffic, PM<sub>2.5</sub> total and traffic as in the percent predicted analysis  
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5 222 (Table S3 and Table 3). However, in this analysis PM<sub>10</sub> and PM<sub>BC</sub> from industry were also associated  
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7 223 with decreased FEV<sub>1</sub> and FVC (Table S3). In a logistic regression, high exposure to any particle fraction  
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9 224 from traffic were associated with increased odds ratio of having clinically significant reductions in FEV<sub>1</sub>  
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11 225 and FVC (below LLN) ( $p < 0.05$ ; except  $p = 0.08$  for FEV<sub>1</sub> and PM<sub>BC</sub>) (Table S4). The ratio FEV<sub>1</sub>/FVC below  
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13 226 LLN was not associated with any exposure (data not shown).  
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### 17 227 **Genetic main effects**

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20 228 All SNPs were in Hardy-Weinberg equilibrium except rs1136450, which has one very rare genotype  
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22 229 ( $n = 12$ ). The frequency of the dominant minor allele carrier genotype varied from 12.6% to 68.0%.  
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24 230 (Table S5). In a main effect analysis without considering environmental exposure, minor allele carrier  
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26 231 status of three GST SNPs was associated with lung function outcomes in minor allele dominant genetic  
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28 232 models. The two GSTP1 SNPs rs762803 and rs1695 were significantly associated with FEV<sub>1</sub> reductions  
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30 233 by -0.80% ( $p = 0.044$ ) and -0.90% ( $p = 0.017$ ), respectively, and FVC reductions were seen in minor allele  
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32 234 carriers of the same GSTP1 SNP rs762803 (-0.74%,  $p = 0.042$ ) and the GSTT1 null genotype assessed with  
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34 235 SNP rs2266637 (-1.434%,  $p = 0.001$ ). No main effect associations were found with SP-A SNPs (Table S5).  
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### 39 236 **Effect modification of PM effects**

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42 237 PM<sub>2.5</sub>, which had marginally more consistent effects for traffic-related exposure, was used for  
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44 238 exploratory interaction analyses. The effect of genotype and exposure to PM<sub>2.5</sub> from all sources was  
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46 239 analysed in interaction models, and SNPs with exposure-interaction  $p$ -values below 0.1 are shown in  
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48 240 Table S6. The number of significant interactions was higher than expected by chance. The most  
49  
50 241 plausible statistically significant patterns of interaction were seen for industry-related exposure (Figure  
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52 242 2). Two SNPs from SP-A1, rs1136451 and rs1059057 had significant interaction effects on both FEV<sub>1</sub>  
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54 243 and FVC, and on FVC only, respectively, suggesting variable susceptibility at high exposures. This result  
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56 244 should, however, be seen as highly exploratory. Analysing the data stratifying by smoking status, atopy,  
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58 245 asthma status, and BMI category showed no significant effect modification on the estimated effect of  
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3 246 PM2.5 from traffic sources on lung function in either linear or logistic analysis. Although the estimated  
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5 247 effect of exposure differed between the subgroups, all confidence intervals overlapped (Table S7).  
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**DISCUSSION**

In a general population cohort we observed significant associations between lung function and modelled exposure to PM<sub>10</sub> and PM<sub>2.5</sub> from traffic as well as PM<sub>BC</sub>. The association between FEV<sub>1</sub> 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 90<sup>th</sup> percentile) compared to low exposure (<50<sup>th</sup> 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<sub>1</sub> below LLN was associated with high exposure to PM<sub>10</sub> and PM<sub>2.5</sub> traffic particles, and FVC below LLN was associated with traffic particles in all size fractions as well as total PM<sub>BC</sub> (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<sub>1</sub> 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.<sup>29 36</sup> Interestingly, in the analysis of crude lung function (in mL, rather than percent of predicted) we also observed associations with particles of

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3 272 industrial origin, suggesting that they could be modified by factors related to age, height and sex which  
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5 273 are accounted for in the percent predicted value.  
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8 274 In spite of there being moderate to high correlations (0.75, 0.42 and 0.99) between total PM and traffic  
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10 275 related PM in any of the three fractions (Table S1), total PM<sub>10</sub> and PM<sub>2.5</sub> were not significantly  
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12 276 associated with reductions in percent predicted FVC and FEV<sub>1</sub>. Residential heating is the second largest  
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14 277 local contribution to total PM, and we observed negative correlations between PM from residential  
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16 278 heating and total PM as well as PM from other sources. PM from residential heating could thus be  
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18 279 interpreted as an indicator of low exposure to other sources of air pollution which might contribute to  
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20 280 explaining the few suggested inverse (positive) associations seen in some categorical analyses between  
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22 281 PM from residential heating and FEV<sub>1</sub> and FVC (e.g. Figure 1).  
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27 282 For GSTP and GSTT genotypes, where carrying the minor or null allele, were associated with decreased  
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29 283 percent predicted FEV<sub>1</sub> and FVC, whereas no direct effects of SP-ASNPS were found (Table S4). Gene-  
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31 284 environment interactions were tested for all SNPs and all PM sources and size fraction, but significant  
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33 285 and biologically plausible interactions were only observed between specific SP-A SNPs and exposure  
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35 286 to PM<sub>2.5</sub> from marine traffic and industrial sources, and not for traffic or total PM, where most direct  
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37 287 effects were observed. We thus infer that it is possible that detrimental effects from marine traffic  
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39 288 and industry PM t may affect specific individuals with genetic susceptibilities.<sup>14</sup> Industrial exposure in  
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41 289 Gothenburg is concentrated along the northern mouth of the Göta Älv River and is dominated by a  
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43 290 power plant and oil refineries. PM from marine traffic is also concentrated along the river.  
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48 291 During initial analysis and covariate selection, we found that residential region was an effect modifier,  
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50 292 and included this as a covariate in the study. Other studies of lung function within a single region have  
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52 293 adjusted for municipality to avoid confounding of the results which is likely due socio-economic  
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54 294 distribution of the study population in some urban areas, where high-exposed areas also have a high  
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56 295 proportion of individuals with high socio-economic status which entails other risk factor panorama and  
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58 296 health behaviours.<sup>37</sup>  
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3 297 In a previous study on the same cohort population, short distance to the nearest road was found to be  
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5 298 associated with decreases in FEV<sub>1</sub> and FVC.<sup>38</sup> Comparing with other studies, the size of the estimated  
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7 299 change in lung function in our study are similar and within confidence intervals of those reported from  
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10 300 the UK biobank.<sup>3</sup> The pollution levels found in the current study were moderate compared to those  
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12 301 presented in the study from Adam and colleagues, reporting significant associations for both FEV<sub>1</sub> and  
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14 302 FVC in adults related to long term exposure to NO<sub>2</sub>, NO<sub>x</sub> and PM<sub>10</sub>, but not PM<sub>2.5</sub> or coarse PM in a  
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16 303 meta-analysis of the ESCAPE data.<sup>7</sup> In our study, both of NO<sub>x</sub> and NO<sub>2</sub> were highly correlated with  
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18 304 traffic PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (all correlations  $r > 0.79$ ), for the years that both NO<sub>x</sub> and NO<sub>2</sub> and source  
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21 305 specific PM estimates were available.

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24 306 Effects specifically of exposure to industrial emissions have not been widely studied, and industry  
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26 307 emissions are often pooled with other sources,<sup>29</sup> or considered negligible as high stacks disperse the  
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28 308 emissions.<sup>39</sup> Studies of respiratory health with source specific results generally find associations mainly  
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30 309 with traffic: In the study of Jacquemin and colleagues,<sup>8</sup> only traffic, and not industry-specific particles  
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32 310 were associated with the lung damage marker CC16. Krall and colleagues<sup>13</sup> observed only effects from  
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34 311 tailpipe exhaust on lung function and eNO. Billet and colleagues<sup>9</sup> exposed cells *in-vitro* to particles from  
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36 312 a highly industrialized environment and found that ultrafine particles with higher concentrations of  
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38 313 polyaromatic hydrocarbons induced more oxidative DNA damage adducts and DNA damage response.  
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41 314 Peng and colleagues<sup>6</sup> observed that PM from vehicle emissions, diesel engines and wood burning were  
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43 315 associated with the largest increases in emergency hospital admissions for CVD and respiratory  
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45 316 disease.<sup>6</sup> In a multi-city European study<sup>40</sup> there were negative associations between FEV<sub>1</sub> and PM from  
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47 317 nickel and sulphur, however results were not consistent between cities, perhaps reflecting the  
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49 318 heterogeneity in particle compositions in different cities in the study.<sup>41</sup>

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54 319 SP-A has the ability to bind and help clear pathogens but also particle matter from the lungs by  
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56 320 opsonisation<sup>22</sup> and is activated in response to exposure to Ozone, another major air pollutant<sup>42</sup>  
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58 321 Previous literature suggest that SNPs of SP-A are associated with defect opsonisation, and hence  
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3 322 increased risk for viral infections,<sup>43</sup> but likely also for adverse effects of particle exposure (as well as  
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5 323 volatile exposures.<sup>22</sup> We found a significant interaction between polymorphisms of two SP-A1 SNPs  
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7 324 and the association between exposure to PM from industrial sources and lung function. Other studies  
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9 325 have found rs1059057 to be associated with acute lung injury<sup>22</sup> and cystic fibrosis,<sup>44</sup> and rs1136451  
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11 326 with susceptibility to COPD and analysed gene-environment effects from tobacco smoking.<sup>24</sup> The SP-A  
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14 327 2 SNP rs4253527 has been associated with tuberculosis.<sup>22</sup>

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17 328 We observed no gene-environment interactions with any GSTT or GSTP SNPs. The GSTP SNP rs1695  
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19 329 has been associated with possible increased asthma risk of air pollution exposure,<sup>19</sup> whereas we found  
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21 330 a main effect with lower FEV<sub>1</sub> in the current study of adults, but no interactions. These genetic  
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23 331 interactions results should be seen as exploratory and be interpreted with caution.

### 24 25 26 27 332 **Strengths and limitations**

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29 333 The cohort data used in this study were collected to study respiratory health, and provides a rich  
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31 334 dataset containing a large number of variables of interest. In the model selection, adding additional  
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33 335 covariates as potential confounders did not affect the regression estimates substantially.  
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35 336 Nonparticipation analysis was previously reported for the earliest collected cohort data (gathered  
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37 337 2001–2003) and showed that women, the elderly, and individuals with university education were more  
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39 338 likely to participate.<sup>28</sup> As we adjusted for these covariates and as exposure was unknown to  
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41 339 participants, this is not likely to bias the current results.

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45 340 The number of individuals who fell below the lower limit of normal for both FEV<sub>1</sub> and FVC was rather  
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47 341 high, as this value is defined as the 5<sup>th</sup> percentile in a healthy, non-smoking population. It is possible  
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49 342 that individuals with respiratory issues, as well as past and present smokers, are more likely to take  
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51 343 part in a study such as ADONIX.<sup>28</sup> On the other hand, with clinical outcome measures and an exposure  
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53 344 which was not known to the participants, this is an unlikely source of important bias.

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57 345 In this study, complete residential histories, including duration of residence, were not available.  
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59 346 Instead, we used a single modelled value for residential exposure that was matched by year of

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3 347 participation for each individual, rather than a complete longitudinal exposure history over multiple  
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5 348 years. We consider this a reasonable approach, as the between-year correlation in air pollution  
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7 349 concentrations and emissions in a certain location is very high.  
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10 350 As people spend a fair proportion of their time outside their home, and our results are based on  
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12 351 modelled air pollution data at the place of residence, the exposure represents an approximation of the  
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14 352 real exposure. However, this is an established method which provides a fair picture of the actual  
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16 353 exposure. The resulting, and likely nondifferential, misclassification of exposure would, however, then  
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18 354 to shrink risk estimates towards the null. The model was developed using new emissions inventories,  
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20 355 updated information on vehicle composition, and had been further verified by measurements.<sup>29</sup>  
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22 356 However, for residential heating, the source assignment is based on proxies such as building type, as  
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24 357 no actual source inventory was available, and may have a poorer performance.  
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29 358 The very high correlations between traffic-related PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>BC</sub> (Table S1) mean that it is  
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31 359 difficult to assign the observed effect to a certain size fraction with any certainty. The moderate to  
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33 360 high correlations between the various PM source measures also meant we had to refrain from using  
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35 361 multi-pollutant models, meaning that the estimates associated with each exposure type must be  
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37 362 interpreted cautiously. Nevertheless, traffic-related PM exposure showed clear and consistent  
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39 363 associations with FEV<sub>1</sub> and FVC, whereas the other source-specific exposures did not.  
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## 43 364 **CONCLUSION**

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46 365 In this large study of clinically measured outcomes in a general population sample we found that  
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48 366 exposure to traffic particles of all three studied PM species and size fractions were associated with  
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50 367 reductions in FEV<sub>1</sub> and FVC and increased risk of low FEV<sub>1</sub> and FVC (below LLN), supporting the need  
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52 368 for measures to reduce urban pollution from traffic to protect urban populations. Furthermore, we  
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54 369 found intriguing suggestions in our exploratory analysis that the SP-A1 gene may play a part in  
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56 370 susceptibility to air pollution from industrial sources, possibly due to its very different composition.  
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3 371 **Author Contributions**  
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5 372 HKC analysed the data and drafted the manuscript. FN, KT, and A-CO provided the cohort  
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7 373 and genetic data, contributed to essential parts of the introduction and discussion and the final  
8  
9 374 manuscript. DS provided and documented the PM exposure data. All authors approved the  
10  
11 375 final version of the manuscript and contributed to the discussion.

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13 376 **Data statement**  
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15 377 Additional data from the ADONIX study exist and are held by the authors.  
16

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19  
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21  
22 380 Council Formas, The Swedish Society for Medical Research and the Swedish Environmental  
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24 381 Protection Agency.

25 382 **Competing interests**  
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27  
28 383 None declared.  
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30 384 Ethics approval: The Västra Götaland Region ethical review board approved of the study (ref  
31  
32 385 no. Ö 092-01) and participants gave informed consent.  
33

34 386 **Legends**  
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37 387 Figure 1 Change in FEV<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50<sup>th</sup> to  
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39 388 90<sup>th</sup>) and high (above 90<sup>th</sup> percentile) concentration of source-specific PM  
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43 390 Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV<sub>1</sub> and  
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45 391 FVC in exposure categories to select PM sources. Dotted lines represent effects on minor  
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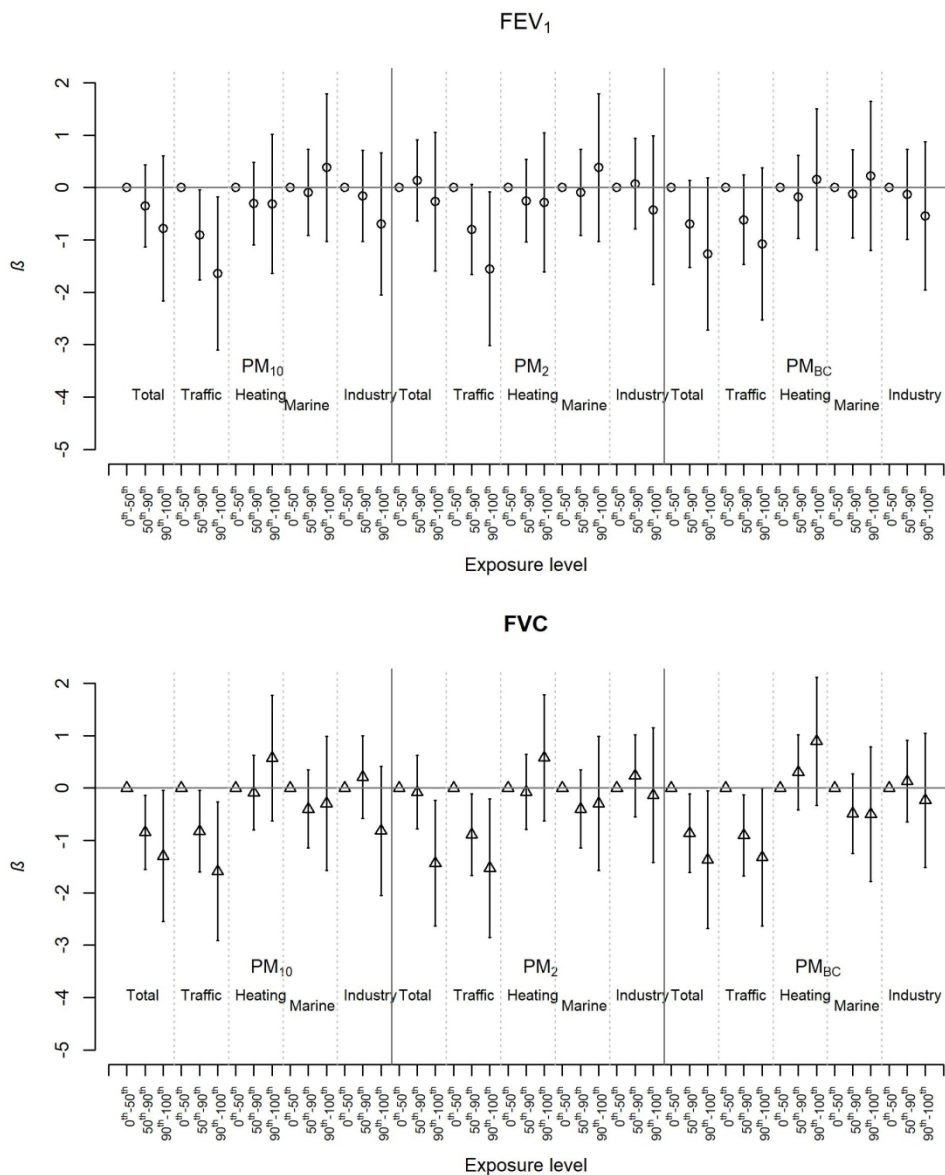


Figure 1 Change in FEV<sub>1</sub> and FVC (% predicted) associated with exposure to medium (50th to 90th) and high (above 90th percentile) concentration of source-specific PM

169x203mm (300 x 300 DPI)

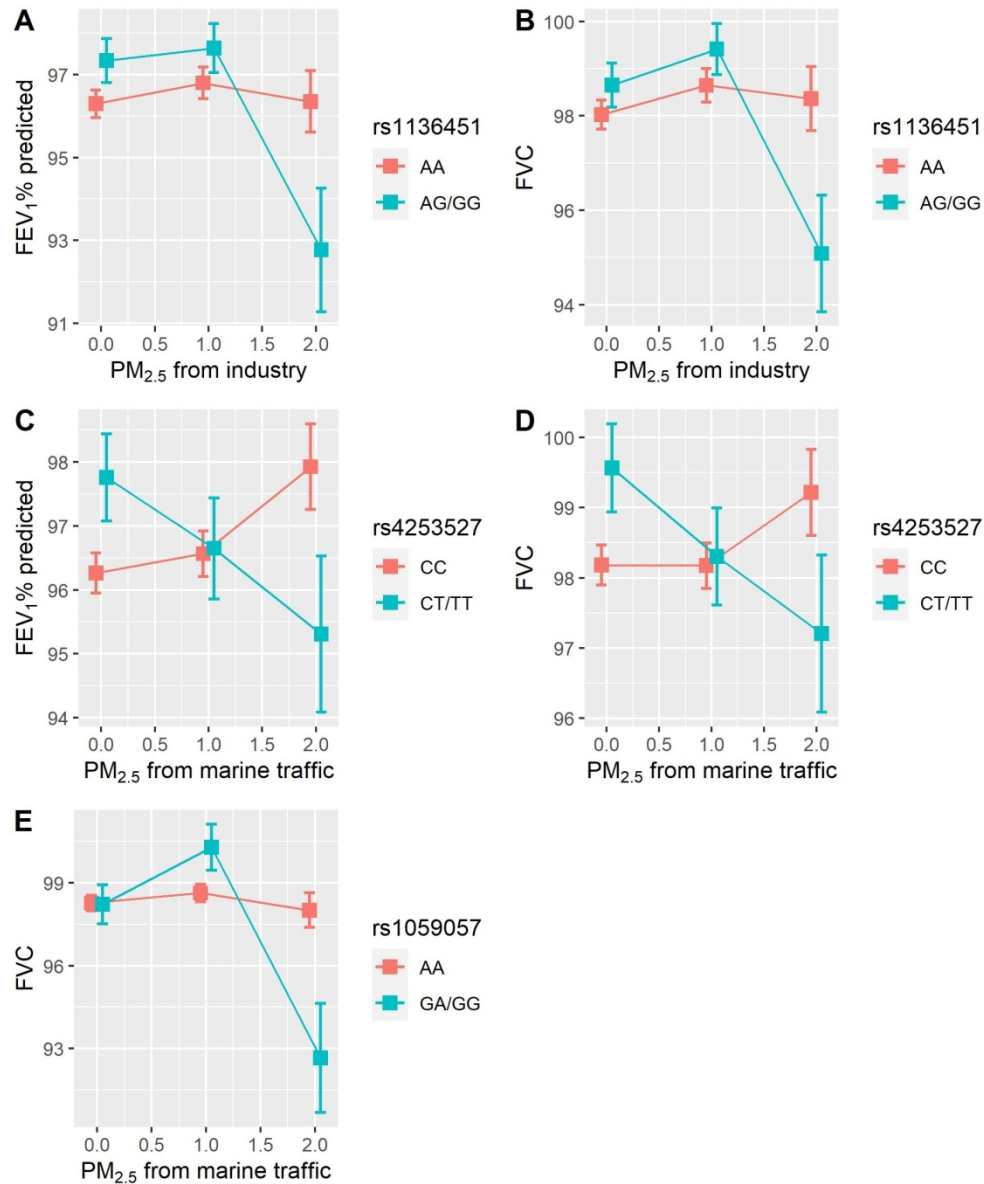


Figure 2 a-e Unadjusted gene-environment interactions between selected SNPs and FEV<sub>1</sub> and FVC in exposure categories to select PM sources with standard error bars. Dotted lines represent effects on minor allele carriers

169x203mm (300 x 300 DPI)

Supplementary tables for ADONIX: Lung function and source specific PM

**Table S1 Correlation (Pearson's) matrix of exposure**

		PM <sub>10</sub>					PM <sub>2.5</sub>					PM <sub>BC</sub>				
		Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry	Total	Traffic	Res. heating	Marine traffic	Industry
PM <sub>10</sub>	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 <sub>2.5</sub>	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 <sub>BC</sub>	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<sub>1</sub> and FVC (% predicted) across exposure strata from low (0-50<sup>th</sup> percentile) to high (above 90<sup>th</sup> percentile) concentrations of source-specific PM (Figure 1)**

	FEV <sub>1</sub>				FVC			
	$\beta$	95% CI		$p$	$\beta$	95% CI		$p$
		Lower	Upper			Lower	Upper	
<b>PM<sub>10</sub></b>								
Total	-0.37	-0,97	0,22	0.22	<b>-0.73</b>	-1,27	-0,19	<b>0.01</b>
Traffic	<b>-0.85</b>	-1,51	-0,19	<b>0.01</b>	<b>-0.81</b>	-1,40	-0,21	<b>0.01</b>
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
<b>PM<sub>2.5</sub></b>								
Total	-0.03	-0,60	0,54	0.92	-0.47	-0,98	0,05	0.08
Traffic	<b>-0.79</b>	-1,45	-0,13	<b>0.02</b>	<b>-0.81</b>	-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
<b>PM<sub>BC</sub></b>								
Total	<b>-0.66</b>	-1,30	-0,01	<b>0.05</b>	-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<sub>1</sub> and FVC (mL) per IQR change in PM exposure**

	IQR ( $\mu\text{g}/\text{m}^3$ )	FEV <sub>1</sub>			FVC		
		$\beta$	95% CI		$\beta$	95% CI	
			Lower	Upper		Lower	Upper
<b>PM<sub>10</sub></b>							
Total	3.05	-23	-46	0	-11	-30	8
Traffic	1.64	<b>-23</b>	<b>-43</b>	<b>-4</b>	<b>-20</b>	<b>-36</b>	<b>-4</b>
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-8	16	4	-6	13
Industry	0.10	<b>-26</b>	<b>-47</b>	<b>-5</b>	<b>-18</b>	<b>-35</b>	<b>-1</b>
<b>PM<sub>2.5</sub></b>							
Total	2.47	<b>-28</b>	<b>-54</b>	<b>-3</b>	-5	-26	15
Traffic	0.52	<b>-24</b>	<b>-43</b>	<b>-5</b>	<b>-20</b>	<b>-36</b>	<b>-4</b>
Residential heating	0.62	4	-20	28	-7	-27	12
Marine traffic	0.03	4	-38	46	4	-30	38
Industry	0.06	<b>-24</b>	<b>-49</b>	<b>0</b>	<b>-18</b>	<b>-38</b>	<b>2</b>
<b>PM<sub>BC</sub></b>							
Total	0.33	<b>-29</b>	<b>-50</b>	<b>-8</b>	<b>-25</b>	<b>-42</b>	<b>-7</b>
Traffic	0.25	<b>-24</b>	<b>-42</b>	<b>-6</b>	<b>-18</b>	<b>-33</b>	<b>-4</b>
Residential heating	0.07	4	-21	28	-11	-31	8
Marine traffic	0.01	3	-8	15	3	-6	13
Industry	0.01	<b>-27</b>	<b>-51</b>	<b>-2</b>	<b>-20</b>	<b>-40</b>	<b>0</b>

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<sub>1</sub> and FVC below LLN in medium and high exposure strata by PM source and size fraction\***

Model	Percentile	LLN FEV <sub>1</sub>				LLN FVC			
		OR	95% CI		p	OR	95% CI		p
			lower	upper			lower	upper	
<b>PM<sub>10</sub></b>									
Total	0-50 <sup>th</sup>	-	-	-	-				
	50 <sup>th</sup> -90 <sup>th</sup>	1.05	0.87	1.26	0.61	<b>1.23</b>	<b>1.00</b>	<b>1.51</b>	<b>0.05</b>
	90 <sup>th</sup> -100 <sup>th</sup>	1.18	0.86	1.62	0.31	<b>1.40</b>	<b>0.98</b>	<b>1.99</b>	<b>0.06</b>
Traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.12	0.92	1.36	0.28	1.16	0.93	1.45	0.18
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.46</b>	<b>1.06</b>	<b>2.02</b>	<b>0.02</b>	<b>1.45</b>	<b>1.00</b>	<b>2.08</b>	<b>0.05</b>
Residential heating	0-50 <sup>th</sup>	ref	-	-	-		ref	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.04	0.87	1.25	0.65	1.02	0.83	1.25	0.87
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.66	1.25	0.54	0.69	0.47	1.01	0.06
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.99	0.81	1.22	0.95	1.03	0.82	1.30	0.79
	90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.32	0.85	1.13	0.79	1.61	0.49
<b>PM<sub>2.5</sub></b>									
Total	0-50 <sup>th</sup>								
	50 <sup>th</sup> -90 <sup>th</sup>	0.97	0.81	1.16	0.76	1.03	0.84	1.26	0.77
	90 <sup>th</sup> -100 <sup>th</sup>	1.07	0.79	1.46	0.66	1.31	0.94	1.82	0.11
Traffic	0-50 <sup>th</sup>	ref	-	-	-				
	50 <sup>th</sup> -90 <sup>th</sup>	1.13	0.93	1.38	0.22	1.21	0.97	1.51	0.09
	90 <sup>th</sup> -100 <sup>th</sup>	<b>1.47</b>	<b>1.06</b>	<b>2.03</b>	<b>0.02</b>	<b>1.54</b>	<b>1.07</b>	<b>2.21</b>	<b>0.02</b>
Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	1.03	0.85	1.23	0.79	1.02	0.83	1.25	0.87
	90 <sup>th</sup> -100 <sup>th</sup>	0.90	0.65	1.23	0.50	0.69	0.47	1.01	0.06
Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	0.98	0.81	1.18	0.82	1.01	0.82	1.26	0.89
	90 <sup>th</sup> -100 <sup>th</sup>	0.83	0.59	1.17	0.29	0.91	0.62	1.33	0.64
Industry	0-50 <sup>th</sup>					ref	-	-	-
	50 <sup>th</sup> -90 <sup>th</sup>	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

1		90 <sup>th</sup> -100 <sup>th</sup>	0.97	0.71	1.33	0.83	1.13	0.79	1.61	0.49
2	<b>PM<sub>BC</sub></b>									
3		Total					ref	-	-	
4		0-50 <sup>th</sup>								
5		50 <sup>th</sup> -90 <sup>th</sup>	1.08	0.89	1.31	0.44	1.07	0.86	1.32	0.56
6		90 <sup>th</sup> -100 <sup>th</sup>	1.34	0.97	1.86	0.08	<b>1.46</b>	<b>1.02</b>	<b>2.09</b>	<b>0.04</b>
7	Traffic	0-50 <sup>th</sup>	ref	-	-	-				
8		50 <sup>th</sup> -90 <sup>th</sup>	1.17	0.96	1.42	0.12	1.19	0.95	1.48	0.13
9		90 <sup>th</sup> -100 <sup>th</sup>	1.37	0.98	1.90	0.06	<b>1.55</b>	<b>1.08</b>	<b>2.23</b>	<b>0.02</b>
10	Residential heating	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
11		50 <sup>th</sup> -90 <sup>th</sup>	1.09	0.90	1.30	0.38	0.94	0.76	1.15	0.54
12		90 <sup>th</sup> -100 <sup>th</sup>	0.80	0.57	1.11	0.18	<b>0.64</b>	<b>0.44</b>	<b>0.94</b>	<b>0.02</b>
13	Marine traffic	0-50 <sup>th</sup>	ref	-	-	-	ref	-	-	
14		50 <sup>th</sup> -90 <sup>th</sup>	1.00	0.82	1.21	0.96	1.00	0.81	1.25	0.98
15		90 <sup>th</sup> -100 <sup>th</sup>	0.89	0.64	1.26	0.52	0.94	0.64	1.37	0.75
16	Industry	0-50 <sup>th</sup>					ref	-	-	
17		50 <sup>th</sup> -90 <sup>th</sup>	0.96	0.78	1.17	0.67	1.05	0.84	1.32	0.68
18		90 <sup>th</sup> -100 <sup>th</sup>	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<sub>1</sub>, 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.

Supplementary tables for ADONIX: Lung function and source specific PM

**Table S5 Genetic main effects: Changes in FEV<sub>1</sub> and FVC in minor allele carriers relative to major allele carriers of GSTP, GSTT and SP-A SNPs**

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

## Supplementary tables for ADONIX: Lung function and source specific PM

1										
2		(TT+TC)	848 (18.5)							
3		vs CC	3735 (81.5)	0.479	-0.513	1.471	0.344	0.508	-0.392	1.408
4	<b>SP-A 2</b>									
5		rs1059046								
6		(GG+GT)	2814 (61.8)							
7		vs TT	1741 (38.2)	0.070	-0.724	0.865	0.862	0.038	-0.682	0.759
8		rs1965707								
9		(AA+AG)	2103 (46.2)							
10		vs GG	2449 (53.8)	0.085	-0.686	0.856	0.829	0.255	-0.446	0.956
11		rs1965708 )								
12		(TT+TG)	1551 (33.8)							
13		vs GG	3041 (66.2)	-0.583	-1.397	0.231	0.160	-0.342	-1.08	0.396
14										

With adjustment 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 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
<b>FEV<sub>1</sub></b>						
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	<b>rs1136450</b>	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	<b>0.04</b>	<b>0.01</b>
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	<b>0.02</b>	P>0.1
SP-A2	<b>rs1059046</b>	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
<b>FVC</b>						
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	<b>0.03</b>
GSTT1	rs2266637	0.048	P>0.1	P>0.1	P>0.1	P>0.1
SP-A1	<b>rs1136450</b>	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	<b>0.01</b>
SP-A1	rs4253527	P>0.1	P>0.1	P>0.1	<b>0.03</b>	P>0.1
SP-A2	<b>rs1059046</b>	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	<b>0.03</b>	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.

Supplementary tables for ADONIX: Lung function and source specific PM

**Table S7 Sensitivity analysis - ESTIMATED CHANGE IN FEV<sub>1</sub> AND FVC PER IQR CHANGE IN PM<sub>2.5</sub> FROM traffic in various subgroups of the cohort**

Linear regression	FEV <sub>±</sub>				FVC			
	β	95% CI		p	β	95% CI		p
		Lower	Upper			Lower	Upper	
<u>Smoking status</u>								
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
<u>Atopic sensibilisation*</u>								
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
<u>Asthma*</u>								
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
<u>Body mass index (BMI, kg/m<sup>2</sup>)</u>								
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
<u>Logistic regression</u>								
	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
<u>Smoking status</u>								
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
<u>Atopic sensibilisation*</u>								
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
<u>Asthma**</u>								
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
<u>Body mass index (BMI, kg/m<sup>2</sup>)</u>								

Supplementary tables for ADONIX: Lung function and source specific PM

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

5 FEV<sub>1</sub>, forced expiratory volume in 1 second. FVC, forced vital capacity. IQR, interquartile range. β from linear regression models adjusted for age, weight,  
6 education, area of residence, and smoking status, excluding the stratification variable in the models stratified for smoking status and BMI. ORs from generalized  
7 linear regression models adjusted for age, weight, education, area of residence, and smoking status excluding the stratification variable in the models stratified  
8 for smoking status and BMI.

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

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

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

	Item No	Recommendation	
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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.
<b>Results</b>			
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.
<b>Discussion</b>			
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
<b>Other information</b>			
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.

1 \*Give information separately for exposed and unexposed groups.  
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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
5 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
6 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
7 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
8 available at <http://www.strobe-statement.org>.  
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