Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis

UNIVERSITÀ DEGLI STUDI DI TORINO

Long-term exposure to air pollution and lung function in adults: multicentre cohort study and meta-analysis, the ESCAPE project

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Abstract

Objectives To investigate the association of long-term exposure to ambient air pollution with lung function level and change in adult participants from five cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE).

Design Multicentre cohort study and meta-analysis of the results.

Setting Centres from five cohorts in Belgium, France, Germany, Italy, Spain, Sweden, Switzerland and the United Kingdom

Participants 7613 participants undergoing spirometry twice within a decade were enrolled.

Main outcome measures Residential exposure to nitrogen oxides (NO2, NOx) and particulate matter (PM) was modeled and traffic indicators were assessed in a standardized manner. The spirometric parameters FEV1 and FVC were considered as outcomes. Cohort-specific analyses were performed by mixed linear regression adjusting for sex, age, height, BMI, education and smoking status. Cohort-specific results were combined using meta-analysis.

Results We did not observe an association of air pollution with the longitudinal change in lung function, but we observed that a 10 $\mu g/m^3$ increase in NO_2 exposure was associated with lower levels of FEV_1 (-14.0 mL (95%CI:-25.8,-2.1)) and FVC (-14.9 mL (-28.7,-1.1)). An increase of 10 $\mu g/m^3$ in PM_{10}, but not other PM metrics ($PM_{2.5}$, PM coarse, PM absorbance), was associated with a lower level of FEV_1 (-44.6mL (-85.4,-3.8)) and FVC (-59.0mL (-112.3,-5.6). Higher traffic load at home address was also significantly associated with lower levels of FEV_1. The associations were particularly strong in obese persons.

Conclusions This study adds to the evidence for an adverse association of ambient air pollution with lung function in adults at very low levels in Europe.

Introduction

Lung function specifically, forced vital capacity [FVC] and forced expiratory volume in one second [FEV1]) are objectively measurable quantitative parameters of respiratory health. It is an early indicator of respiratory and systemic inflammation, and associated with cardiorespiratory morbidity and mortality. Acute effects of air pollution on lung function at levels currently observed in Western Europe at all ages are well established. To what extent long-term exposure to air pollution results in lower lung function remains less clear[1]. Evidence for long-term pollution effects on slowing down lung function growth in children is strong, while data for chronic lung function effects in adults is more limited and mostly restricted to susceptible populations [1-3]. In the largest [4] of the predominantly cross-sectional studies [4-7], Forbes et al. found increases in 10 μg/m^3 of PM_{10} associated with a decrease of about 3% in FEV_1. At 1st spirometry SAPALDIA found an increase of 10 μg/m^3 in annual mean concentration of PM_{10} was associated with 3.4% lower FVC and 1.6% lower FEV_1 [5]. The SALIA study of women showed negative associations of PM_{10} concentrations with FEV_1 and FVC (5.1% and 3.7% respectively, per 7 μg/m^3 5-year annual mean PM_{10}) [7]. The strongest indirect evidence for adverse long-term pollution effects on lung function decline in adults comes from a single follow-up study demonstrating that improvements in PM_{10} exposure over a period of eleven years attenuated the age-related decrease in respiratory function [8]. A more recent study found cumulative long-term exposure to ambient PM_{10} and ozone associated with both FEV_1 and FVC decline in an elderly population and suggested an increased susceptibility among frail persons [9]. Statistically significant associations were also reported for NO_2 and traffic exposure [5, 7].

The ESCAPE project (European Study of Cohorts for Air Pollution Effects) combined data from over 30 cohort studies and modeled home outdoor levels of air pollution in a standardized manner [10]. This paper makes use of five health cohorts with spirometry data, to investigate the association of air pollution with lung function level and age-related decline.

Methods

Design and Participants

This study is an analysis of cohort data obtained by ESCAPE to investigate the long term effects of exposure to air pollution on respiratory health in Europe and a meta-analysis of the cohort specific results. The present study included 5 European cohorts/studies from eight countries with information on lung function and the most important potential confounders. The analyses were based on subpopulations from European Community Respiratory Health Survey (ECRHS), French Epidemiological study on Genetics and Environment of Asthma (EGEA), the National Survey of Health and Development (NSHD), Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) and Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) (Supplemental Material: Methods (Cohorts) and Supplemental Table 1). Criteria for inclusion of cohort participants in the present analyses were: at least 20 years old; pre-bronchodilation spirometry data from two different time points approximately one decade apart (referred to as first (1st) and second (2nd) spirometry, respectively); non-missing information for the primary covariates used in the main models (questionnaire-based variables: age, sex, smoking status, education; measured variables: height and BMI (derived from measured height and weight); living in cohort areas selected for ESCAPE monitoring

campaigns; and successfully assigned home outdoor exposure estimates for NO_2/NO_x/Traffic indicators (referred to as NO-population) and PM metrics (a subsample of the NO population, referred to as PM-population). Of 13259 participants with 1st and 2nd spirometry living in ESCAPE monitoring areas, 7615 and 4233, respectively provided complete datasets towards analysis of NO_2/NO_x/Traffic indicators and PM metrics (Supplemental Figures 1a-e).

Exposure data

ESCAPE exposure assessment was described before and is based on fully standardized measurement and modeling protocols (http://www.escapeproject.eu/manuals/) [10-13]. The general concept consisted in the individual assignment of outdoor annual mean concentrations of a pre-defined set of air pollution markers to each participant's residential address.

ESCAPE monitoring campaigns in different study areas between 2008-2011 measured NO_2 and NO_x as well as in a smaller number of areas $PM_{2.5}$, PM_{10}, the coarse fraction of PM (PM_{10} minus $PM_{2.5}$) and light absorbance of $PM_{2.5}$. Within each study area, concentration levels were monitored at 40 (NO_2, NO_x) or 20 (PM measures) predefined sites during three seasonally distinct 2-week periods [13, 14]. Land use regression (LUR) models were developed to explain the spatial variation of measured annual average air pollutant concentration within each study area. This technique combines measurement data with Geographic Information System (GIS) derived land-use and traffic information to predict annual pollution concentration at sites without measurements and was used to estimate annual pollutant concentrations at each participant's residential address [10, 11].

In addition to pollutant concentrations, we also used as indicators of local exposure to traffic related pollutants traffic intensity at the road nearest to a participant's home and total traffic load on major roads in a 100 meter buffer of the home. Traffic measures were often used in other studies as proxies of exposure to near-road pollutants such as e.g. ultrafine particles or NO, which exponentially decay within 100-150 m from the curb side.

To address the time discrepancy between air pollution monitoring (2008-2011) and health examination (spirometry conducted between 1985-2010; Supplemental Table 2), sensitivity analyses replaced ESCAPE exposure estimates with estimates back extrapolated to the time of 1st and 2nd spirometry (except for the time a. of 1st spirometry in ECRHS and EGEA, where no historical data was available and b. 2nd up spirometry in NSHD and SALIA conducted between 2006-2010, sufficiently close to the ESCAPE monitoring campaigns). During the past decades, air quality has in general improved. Given the lack of historic LUR models, ESCAPE could not individually estimate within-city contrasts of air quality for these past years. Instead, where available, annual means from fixed site monitoring stations were used to derive past annual mean concentrations for pollutants with available historic data (NO_2 and PM_{10}, only). For each study participant's home address the back extrapolated concentration was obtained by multiplying the modeled ESCAPE annual mean concentration with the ratio between average annual concentrations as derived from the routine monitoring site(s) for the period in the past and for the ESCAPE measurement period time (for details see in (http://www.escapeproject.eu/manuals/) [12]. The procedures applied assumed that the

within-city spatial contrasts remained proportional over time. Gulliver et al confirmed the validity of this assumption for the United Kingdom [15].

Lung Function Metrics and Outcomes

FEV_1 and FVC were used as outcome metrics. In cross-sectional analysis, we focused on lung function measured at the 2nd spirometry (time point closest to ESCAPE air pollution monitoring). Change in lung function between 1st and 2nd spirometry was assessed as both annual lung function change (mL/year) and annual change in lung function as a percentage of the 1st spirometry value (%/year) (Supplemental Material: Methods (Lung Function Metrics and Outcomes)), with a negative value representing a decline. Data presented are restricted to absolute change as results did not materially differ for percent (%) change as outcome.

Statistical analyses

Firstly, study specific data were analyzed separately following identical analytical procedures. Associations of air pollutants with lung function metrics were estimated using multivariable mixed linear regression models with a random intercept for ESCAPE areas with their own exposure monitoring and modeling. Three confounder models were specified a priori, adjusting for an increasing number of covariates selected on the basis of previous cohort studies of air pollution and lung function and the availability of data for most cohorts, excluding missing values on any of the covariates. The covariate definitions were standardized across studies (see Supplemental Material: Methods). In the absence of materially different effect estimates derived from models adjusting for additional covariates, we chose as main analytic model the one adjusting for age (years), age squared, height (cm), sex, body mass index (BMI, kg/m^2), educational level (low as reference, medium, high), and smoking status (never as reference, ever). Models analyzing traffic exposure indices were additionally adjusting for background NO_2 concentrations. The traffic indicator coefficients are thus assumed to reflect the impact of pollutants highly concentrated along the roads. The median of traffic indicator values across all studies was chosen as cutoff for dichotomizing the continuous traffic exposure (≤5000 and >5000 [cars per day] for traffic intensity on the nearest major road; ≤ 500 and >500 [cars-km driven per day] for the traffic intensity on major roads in a 100m buffer) (Supplemental Material: Methods (Statistical Models). Traffic variables were also analyzed on a continuous scale but this did not produce meaningful results.
Secondly, cohort specific overall and stratum-specific effect estimates obtained by mixed linear regression models were meta-analyzed (Supplemental Material: Methods (Meta-analysis)).

A pre-defined set of variables considering previous evidence and cohort differences was tested for effect modification. We compared the summary estimates of the two opposite subgroups (females vs. males; not obese vs. obese; never vs. ever smokers; never asthma vs. ever asthma) using a Chi^2-test with one degree of freedom. In sensitivity analyses we restricted the analytic model to non-movers and participants aged 30+ (age at 1st spirometry).

Statistical analyses were performed using STATA, version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Study characteristics. Table 1 provides a description of the cohort specific study populations. The average age of the cohorts at the time of 2nd spirometry ranged from 43 years (ECRHS) to 73 years (SALIA). The SALIA population, consisting exclusively of women, exhibited the lowest mean levels of FEV_1 (2.20 L) and FVC (2.91 L) (see Table 1) (for the smaller PM subpopulation and for the cohort-specific lung function distributions stratified by sex, smoking and asthma status see Supplemental Table 3).

Air pollution exposure. Table 2 shows the distribution of the air pollution metrics for each study area. Variance explained by LUR models varied between 55% and 92% for NO_2 and between 68% and 90% for PM_{10} (Supplemental Table 4). Mean exposure was lowest for all air pollution metrics in NSHD. Within-study contrasts were smallest for SALIA and SAPALDIA reflecting the restricted geographic region covered (Supplemental Table 5). The study specific correlations between the exposure metrics were generally highest between NO_2 and NO_x (rho of 0.90-0.98), but moderate to low between pollutants and traffic indicators (Supplemental Table 6). ESCAPE derived exposures were highly correlated with the exposures backextrapolated to the time of the 2nd spirometry ($rho_{NO2} \geq 0.94$; $rho_{PM10} \geq 0.91$), but less strongly correlated with exposures backextrapolated to the 1st spirometry ($0.56 \leq rho_{NO2} \leq 0.92$; $0.47 \leq rho_{PM10} \leq 0.74$).

Association between air pollution and lung function. The main meta-analysis results for associations of each air pollution metric with level and change of lung function are presented in Table 3. No associations between any exposure metric and lung function decline were present, irrespective of covariate adjustment and subgroup (gender, obesity, asthma, smoking). Looking at levels of lung function cross-sectionally, we found higher NO_2 and NO_x exposures to be associated with lower levels of FVC and FEV_1. An increase of 10 $\mu g/m^3$ in NO_2 exposure was associated with a -14.0 mL lower level of FEV_1 (95%CI:-25.8,-2.1) and -14.9 mL lower level of FVC (-28.7,-1.1) (Table 3, Figures 1 and 2). An increase of 20 $\mu g/m^3$ in NO_x exposure was associated with a lower level of FEV_1 by -12.9 mL (-23.8,-2.0) and of FVC by -13.3 mL (-25.9,-0.7) and an increase of 10 $\mu g/m^3$ in PM_{10} was associated with a lower level of FEV_1 (-44.6mL (-85.4,-3.8)) and FVC (-59.0mL (-112.3,-5.7)) (Table 3). The other PM metrics were not associated with lung function level. Higher traffic load on major roads in a 100m buffer from residential address was associated with lower levels of FEV_1 (-32.34mL (-59.30,-5.38)).

Associations observed for NO_2 and PM_{10} with FEV_1 and FVC at 2nd spirometry remained largely unaltered when ESCAPE exposure estimates of NO_2 and PM_{10} in ECRHS, EGEA and SAPALDIA were replaced with NO_2 and PM_{10} estimates backextrapolated to the time point of the 2nd spirometry. The inverse association between PM_{10} and FVC became stronger and statistically significant (Supplemental Table 7).

In subgroup analysis, the NO_2 and NO_x (data not shown) associations with FEV_1 and FVC were particularly observed in obese participants (FEV_1: Figures 3 and 4, FVC: Supplemental Figures 2 and 3) (p-values for heterogeneity obese vs. non-obese: p=0.098 (NO_2/FEV_1) (Figures 3 and 4); p=0.026 (NO_2/FVC) (Supplemental Figures 2 and 3), p=0.050 (NO_x/FVC). All other tested factors (gender, smoking and asthma status) showed no or only weak evidence for

modification of the air pollution lung function associations (NO_2: Supplemental Table 8). The effect modification by obesity was also evident in gender-stratified analyses, with substantially stronger inverse NO_2 and NO_x associations with FEV_1 and FVC, in both obese women and men (NO_2: Supplemental Table 9).

In sensitivity analysis, looking at non-movers and participants aged 30 years or more, we did not find a particular difference to the observed main associations (Supplemental Table 10).

Discussion

This study in adults contributes to the evidence of long-term exposure to ambient air pollution being associated with the level of lung function. The meta-analysis was based on individual-level exposure assessment standardized across different cities and regions in Europe. Impaired lung function characterized by reduced FEV_1, a powerful marker of future morbidity and mortality [16], exhibited the most consistent association with different pollution metrics. It was inversely related to nitrogen oxides, PM_{10} as well as traffic load at the residential address. Our data suggest that obese persons are particularly sensitive to air pollution.

Comparison with other studies

Results from previous cross-sectional studies predominantly relied on exposure measured at the level of a few communities. They point to an inverse association of adult lung function with air pollution and traffic load [1, 6]. But as the measurement and meaning of specific pollution metrics differs between studies their comparative relevance remains inconclusive. This also applies to the current study. According to the site-specific differences in correlations between exposure metrics (Supplemental Table 6) they capture different sources of air pollution and thereby different components. The absence of associations with most of the PM metrics may additionally be rooted in the more limited sample size. PM measurements were only performed in a restricted number of centers. NO_2 which characterizes the spatial variation of traffic related air pollution has been linked with stronger lung function impairment depending on the parameter studied, but evidence for PM effects to be stronger has also been published [3, 7].

The interaction between air pollution exposure and obesity on lung function parallels a recent SAPALDIA report and adds evidence to the interdependence of the two important global epidemics of environmental pollution and obesity [17]. Many studies have demonstrated an association between obesity and lung function. Lung function improves after weight loss in obese persons, and weight gain is associated with lung function decline in asthmatics and in the general population [17-19]. The mechanical effect of excess body fat on lung volumes and airway caliber is well accepted [18]. In addition, inflammatory pathways may play a role, as overweight is associated with an underlying state of oxidative stress and inflammation [17, 20]. Air pollution and obesity seemingly have more than additive effects on systemic inflammation [21, 22]. In animal models, ozone-induced pulmonary injury and inflammation were greater in obese versus lean mice [23, 24]. In humans, acute ozone effects on lung function were more prominent among obese [25, 26].

The null finding investigating the association of air pollution with the change in lung function is consistent with a previous report from the ECRHS cohort [27], but extends the finding to older cohorts. In light of the positive findings for the cross-sectional associations, this null finding may be surprising. Cross-sectional differences are expected to result at least in part from differences in age-related decline. Based on the current results it seems premature to conclude that long-term exposure to air pollution does not affect FEV_1 and FVC decline.

Strengths and weaknesses

Our study benefits from a large number of observations, and the multi-centric design across different European regions, which cover a broad range of different types of environment and climates and a wide age range of participants. Furthermore, the individual-level exposure assessment was harmonised, a common study protocol of exposure and outcome definition was developed and the analytic approach was standardised. However, this study has also several limitations.

Several methodological issues related to outcome and exposure assessment may have biased the longitudinal association. Data from only two spirometry time points and from spirometries conducted in different seasons and times of the day may have decreased the precision in estimating lung function decline. As common in long-term lung function studies, spirometry devices had to be updated with new software or replaced during follow-up. Such changes can be an inherent source of differences in the measured lung function and its temporal change [28]. The inherent limitations in exposure assessment are also amplified in the longitudinal analyses. Most importantly, back extrapolation of residential pollution levels is of prime relevance to properly characterize exposure at 1st spirometry, and then derive the change in exposure over time. Uncertainties with the back extrapolated values may be substantial and if unrelated to the true exposure, may bias findings towards the null. In addition LUR models have inherent limitations. Cross-validation of the LUR's varied across regions [10, 11] and performance of models based on 20 or 40 measurement sites may be overestimated [29, 30].

Additional limitations of the study beyond back extrapolation include the non-availability of information on short-term exposure at the time of spirometry for a sufficient number of sites and pollution metrics. Adjustment for short-term exposure in SAPALDIA did not alter the associations. Heterogeneity of study populations poses a challenge to meta-analysis and makes it difficult to exclude residual confounding and unrecognized effect modification. The associations were not sensitive to the SALIA study consisting exclusively of women and exhibiting the lowest mean levels of lung function (Supplemental Figures 4 and 5 for associations of NO_2 with FEV_1 and FVC in women). Non-participation at follow-up of subjects with low lung function may bias observed associations or limit their generalizability. In SAPALDIA subjects with better lung function were more likely to participate at the 2nd spirometry. But sensitivity analyses using inverse probability weighting to account for non-participation did not alter associations between air pollution and lung function [8].

Conclusion

The current study, which includes a large number of observations from different regions, environments and climates in Europe, and standardized exposure assessment, provides firm

support to an adverse association between ambient air pollution and lung function in adults. Inverse associations could be observed at very low air pollution levels in Europe. The policy relevance of these findings is further strengthened by the observation that obese persons may be particularly susceptible.

What is already known on this topic

- Acute effects of air pollution on lung function at levels currently observed in Western Europe at all ages are well established.
- The association between long term exposure to air pollution and lower lung function in adults remains less clear.

What this study adds

- This paper contributes important evidence towards the EU air quality policy debates.
- In the largest European wide meta-analysis of its kind, we report associations of NO_2, NO_x and PM_{10} with lung function.
- The study provides suggestive evidence for an increased susceptibility of obese persons, pointing to the interdependence of environmental and health policies.

Role of the funding source

The funding source had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors had full access to all data and had final responsibility for the decision to submit the paper.

Competing interests

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics committee approval

All included cohort studies were approved by the institutional medical ethics committees and undertaken in accordance with the Declaration of Helsinki. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Transparency statement

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.Å

Data sharing

Meta-analytic data and statistical code are available from the corresponding author.

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Contributors

MA, NPH drafted the manuscript; BB, BF, JS, UK, FK, AH, NK, NPH contributed to the design of the study; MA, TS, AEC, AM, BJ, VS, CS, JS, UK, FK, AH, NK, NPH contributed to the data analysis plan; MA, TS, AEC; YC, BJ, MS, AV, AM, DK, SD, ZAK, GH, contributed to the statistical script and data analysis; RN, VS, RH, DK, TR, POB, RB, PP, JH, DJ, IP, JS, UK, FK, AH, NK, NPH provided local cohort data; DS, ME, MYT, SV, HCP, MB, JC, MC, ADN, MJN, BF, KDH, CD, UQ, RB, GH, BB contributed to exposure assessment; all co-authors contributed to the interpretation of the results and have read, revised and approved the final version of the submitted manuscript.

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Table 1. Description of cohort-specific study populations. Characteristics [a] are presented for the larger subgroup of participants included in the analysis of NO_2 and NO_x and traffic indicators (Characteristics for the smaller subgroup of participants included in the PM metrics analyses are presented in Supplemental Table 1).

Study	**ECRHS**		**EGEA**		**NSHD**		**SALIA**		**SAPALDIA**	
	N_{total}=3859		**N_{total}=568**		**N_{total}=844**		**N_{total}=580**		**N_{total}=1764**	
1st spirometry	**1991-1993**		**1991-1995**		**1999**		**1985-1994**		**1991-1992**	
2nd spirometry	**2001-2002**		**2003-2007**		**2006-2010**		**2007-2009**		**2002**	
Characteristics	**N/mean**	**%/SD**	**N/mean**	**%/SD**	**N/mean**	**%/SD**	**N/mean**	**%/SD**	**N/mean**	**%/SD**
Female	1981	51.3%	303	53.3%	471	55.8%	580	100.0%	980	55.6%
Age	43.0	7.2	53.1	11.3	63.3	1.1	73.3	3.4	53.2	11.0
BMI [kg/m^3]	25.7	4.6	25.3	4.3	27.7	4.9	27.4	4.5	25.4	4.3
Height [in cm]	168.6	9.5	168.5	8.4	167.4	8.6	162.3	5.5	168.8	9.0
Exsmoker	1064	27.6%	206	36.3%	497	58.9%	99	17.1%	568	32.2%
Current smoker	1224	31.7%	81	14.3%	77	9.1%	18	3.1%	492	27.9%
Pack years at 1st spirometry[b]	7.7	12.0	5.9	10.0	9.1	12.6	2.8	8.4	10.9	17.9
Pack years from 1st to 2nd spirometry[b]	3.9	10.9	1.7	8.3	0.7	2.5	0.6	6.7	3.1	6.5
Medium educational level[b]	1321	34.2%	118	20.8%	439	52.0%	276	47.6%	1121	63.5%
High educational level[b]	1420	36.8%	263	46.3%	102	12.1%	199	34.3%	520	29.5%
Environmental tobacco exposure at home or at work[b]	676	17.5%	233	41.0%	168	19.9%	347	59.8%	119	6.7%
Occupational exposure to dust/fumes or gases[b]	1685	43.7%	125	22.0%	246	29.1%	39	6.7%	460	26.1%
Ever asthma[b,c]	616	16.0%	183	32.2%	83	9.8%	50	8.6%	155	8.8%
FEV_1 [L]	3.47	0.81	3.03	0.85	2.83	0.66	2.20	0.42	3.10	0.82
FVC [L]	4.33	0.10	4.00	1.01	3.57	0.81	2.91	0.54	4.08	1.02
change of FEV_1 [L][d]	-0.026	0.032	-0.028	0.031	-0.022	0.025	-0.020	0.014	-0.033	0.030
change of FVC [L][d]	-0.018	0.040	-0.015	0.037	-0.025	0.034	-0.022	0.019	-0.022	0.041

The table shows the amount of observations (N, and % of total N) for categorical variables, and the mean value (and standard deviation (SD)) in case of continuous variables. [a] Characteristics refer to time point of 2nd spirometry. [b] Information missing on a limited number of subjects. [c] Asthma diagnosed by a physician at 1st and/or at 2nd spirometry. [d] Change in lung function between 1st and 2nd spirometry.

Table 2

Distribution of all exposure estimates (annual averages of ambient air pollutants and traffic indicators), at participants residential addresses in each cohort.

Cohorts	ECRHS			EGEA			NSHD			SALIA			SAPALDIA		
Exposures	**N**	**Mean**	**IQR**	**N**	**Mean**	**IQR**	**N**	**Mean**	**IQR**	**N**	**Mean**	**IQR**	**N**	**Mean**	**IQR**
$PM_{2.5}$ [µg/m^3]	1830	15.9	7.0	342	15.3	2.0	751	9.5	1.5	580	17.8	1.7	729	16.8	1.1
$PM_{2.5absorbance}$ [10^{-5}m^{-1}]	1540	2.0	1.6	148	2.1	1.3	751	1.0	0.3	580	1.4	0.4	729	1.9	0.5
PM_{10} [µg/m^3]	1830	25.8	9.7	342	25.1	4.0	751	15.7	1.9	580	26.7	2.1	729	23.2	2.3
PM_{coarse} [µg/m^3]	1830	10.3	4.7	342	9.4	3.3	751	6.4	0.8	580	9.4	1.6	729	6.5	1.9
NO_2 [µg/m^3]	3859	28.9	18.7	568	27.4	14.7	844	22.4	10.0	580	27.6	8.1	1764	27.0	7.7
NO_x [µg/m^3]	3859	50.5	34.5	568	46.7	27.9	844	37.5	17.1	580	44.2	20.7	1764	44.8	15.2
Traffic intensity on nearest road [cars/day]	2492	4807	5509	568	6633	6667	844	1239	0	580	1642	0	1697	3207	3876
Traffic load on nearest major road [cars-km/day; in thousand][a]	2687	1.45	1.67	568	1.37	1.58	844	0.27	0	580	0.72	0.32	1671	0.94	1.42
NO_2 (backextrapolated to 1st spirometry) [µg/m^3]	-[b]	-[b]	-[b]	-[b]	-[b]	-[b]	841	26.3	11.2	580	36.0	14.0	1762	47.7	12.3
PM_{10} (backextrapolated to 1st spirometry) [µg/m^3]	-[b]	-[b]	-[b]	-[b]	-[b]	-[b]	748	22.0	2.6	580	47.7	13.6	726	46.2	4.0
NO_2 (backextrapolated to 2nd spirometry) [µg/m^3]	3859	34.2	23.0	568	32.1	17.5	-[c]	-[c]	-[c]	-[c]	-[c]	-[c]	1764	31.0	8.0
PM_{10} (backextrapolated to 2nd spirometry) [µg/m^3]	1388	27.1	8.4	148	27.0	5.3	-[c]	-[c]	-[c]	-[c]	-[c]	-[c]	729	37.8	4.3

$PM_{2.5}$: particulate matter with a diameter of 2.5 micrometers or less; $PM_{2.5}$abs: absorbance of particulate matter with a diameter of 2.5 micrometers; PM_{10}: particulate matter with a diameter of 10 micrometers or less; PM_{coarse}: coarse fraction of $PM_{2.5}$ to PM_{10}; NO_2: nitrogen dioxide; NO_x: nitrogen oxides. [a] Traffic load on nearest major road within a 100m buffer presented in thousands. [b] No complete exposure backextrapolation to 1st spirometry available. [c] No backetrapolation applied as time point of 2nd spirometry coincides with time point of ESCAPE monitoring campaign.

Table 3:

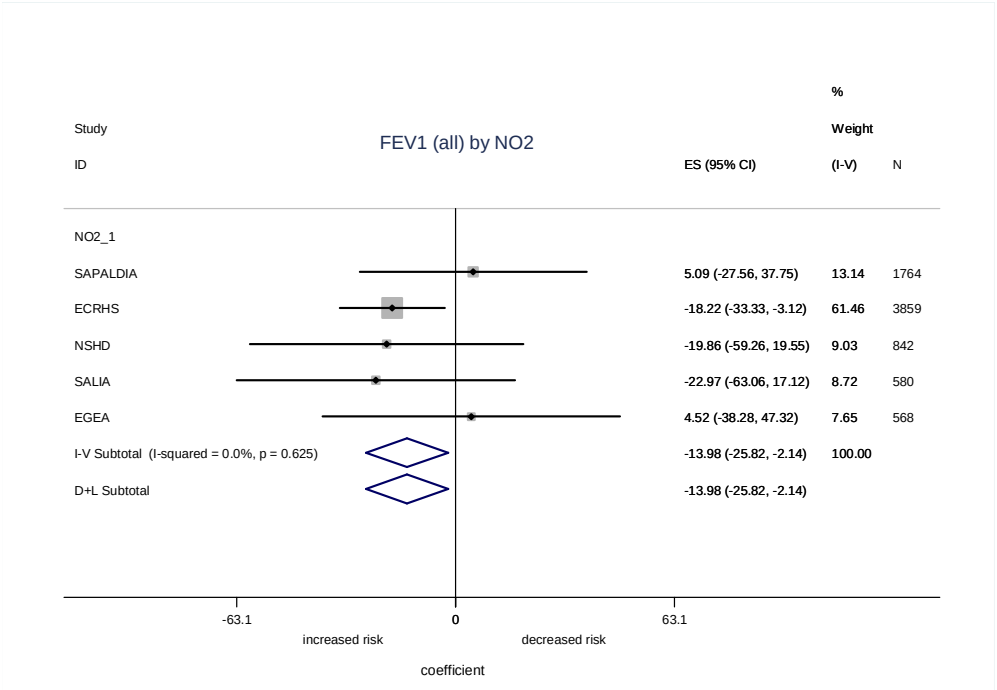
Results of meta-analyses for the association [a] between level (upper part of table) and change (lower part of table) of lung function and exposure to air pollution and traffic intensity indicators.

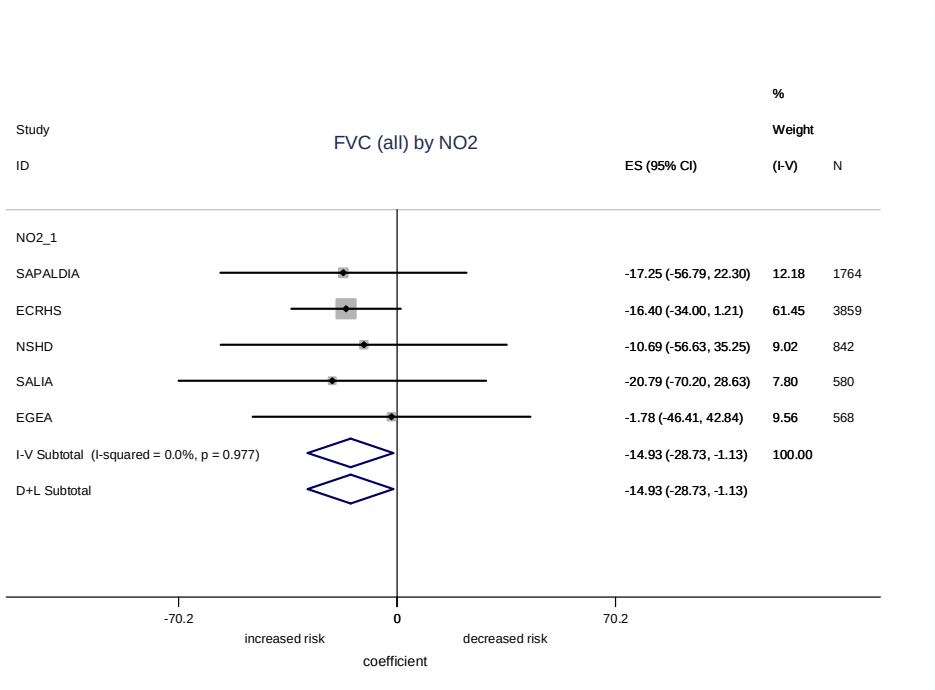
Level of lung function[b]		**FEV_1 (in mL)**			**FVC (in mL)**	
Exposure	**beta[c]**	**95%CI**	**$I^{2\,f}$ p-value$_{het}$**	**beta[c]**	**95%CI**	**$I^{2\,f}$ p-value$_{het}$**
NO_2 (10 µg/m³)	-13.98	-25.82 to -2.14	0.0% p=0.625	-14.93	-28.73 to -1.13	0.0% p=0.977
NO_x (20 µg/m³)	-12.91	-23.79 to -2.04	0.0% p=0.861	-13.25	-25.85 to -0.65	0.0% p=0.962
PM_{10} (10 µg/m³)	-44.56	-85.36 to -3.76	0.0% p=0.628	-58.96	-112.27 to -5.65	0.0% p=0.785
$PM_{2.5}$ (5 µg/m³)	-21.14	-56.37 to 14.08	0.0% p=0.535	-36.39	-83.29 to 10.5	0.0% p=0.877
$PM_{2.5absorbance}$ ($10^{-5}m^{-1}$)	-24.40	-55.58 to 6.79	0.0% p=0.709	-12.94	-50.23 to 24.3	0.0% p=0.619
PM_{coarse} (5 µg/m³)	-22.36	-94.00 to 49.27	12.6% p=0.333	2.88	-87.85 to 93.6	0.0% p=0.760
Traffic intensity on nearest road[e]	-27.61	-59.62 to 4.39	29.0% p=0.228	-10.37	-48.23 to 27.49	27.3% p=0.239
Traffic load on nearest major road in a 100m buffer[e]	-32.34	-59.30 to -5.38	0.0% p=0.784	-18.64	-50.22 to 12.94	0.0% p=0.967
Change in lung function		**FEV_1 (in mL/year)**			**FVC (in mL/year)**	
Exposure	**beta[d]**	**95%CI**	**$I^{2\,f}$ p-value$_{het}$**	**beta[d]**	**95%CI**	**$I^{2\,f}$ p-value$_{het}$**
NO_2 (10 µg/m³)	0.30	-0.39 to 0.98	0.0% p=0.681	0.02	-0.84 to 0.88	0.0% p=0.532
NO_x (20 µg/m³)	0.18	-0.44 to 0.80	0.0% p=0.708	-0.09	-0.86 to 0.69	0.0% p=0.804
PM_{10} (10 µg/m³)	-0.39	-2.85 to 2.06	53.1% p=0.074%	-1.42	-4.53 to 1.70	28.4% p=0.232
$PM_{2.5}$ (5 µg/m³)	-0.14	-2.26 to 1.98	23.8% p=0.263	-1.37	-4.04 to 1.29	0.0% p=0.964
$PM_{2.5absorbance}$ ($10^{-5}m^{-1}$)	0.88	-0.76 to 2.52	54.5% p=0.066	1.14	-0.95 to 3.24	4.5% p=0.381
PM_{coarse} (5 µg/m³)	0.26	-3.92 to 4.43	61.7% p=0.034	-1.31	-6.49 to 3.88	0.0% p=0.506
Traffic intensity on nearest road[e]	-0.74	-2.58 to 1.10	0.0% p=0.772	-0.15	-2.49 to 2.18	18.1% p=0.299
Traffic load on nearest major road in a 100m buffer[e]	-0.32	-1.81 to 1.18	0.0% p=0.987	0.34	-1.56 to 2.25	0.0% p=0.672

[a]Associations are presented for the following increments in exposure: 10 µg/m³ for NO_2, 20 µg/m³ for NO_x, $1*10^{-5}m^{-1}$ for $PM_{2.5}$ absorbance, 5 µg/m³ for $PM_{2.5}$, 10 µg/m³ for PM_{10}, 5 µg/m³ for PM_{coarse}, traffic intensity on the nearest street (2 categories: low ≤5000 and high>5000 [cars/day]); and for traffic load on major roads within a 100 m buffer (2 categories: low ≤ 500 and high>500 [cars-km/day]). [b] Level of lung function for cross-sectional analysis was derived from 2nd spirometry. [c] The betas for the association between level of lung function and exposure, are adjusted for age, age squared, height, sex, BMI, highest educational level, and smoking status at 2nd spirometry; a negative sign indicates lower lung function with increasing exposure. [d] the betas of the association between change in lung function and exposure, are adjusted for sex, age and height at 1st spirometry, highest educational level, smoking at 1st spirometry, smoking cessation and change in BMI to the 2nd spirometry; a negative sign indicates steeper lung function decline with increasing exposure. [e] associations with traffic intensity (2 categories: low ≤5000 and high>5000 [cars/day]) and traffic load (2 categories: low ≤ 500 and high>500 [cars-km/day]) were additionally adjusted for background NO_2 concentrations. [f] I^2 and Cochran's test for heterogeneity of effect estimates between cohorts.

Figure 1 and Figure 2

Forest plot displaying the study-specific mixed linear regression model estimates [a,b] of the association of NO_2 with **level of lung function** (FEV_1; FVC; in mL) (Based on all study participants living in sites with ESCAPE models available).

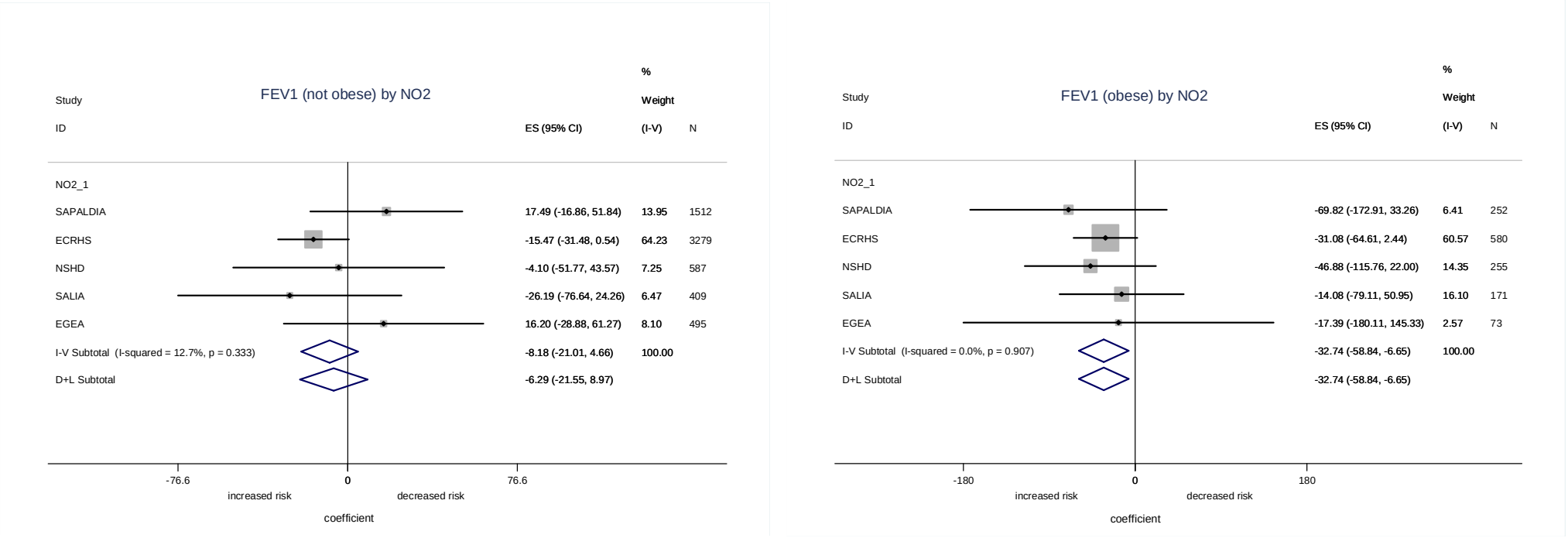




NO_2_1 indicates NO_2 measured at time of ESCAPE. [a] Associations with lung function measures are presented as increments in NO_2 per 10µg/m^3. I-square: variation in estimated effects attributable to heterogeneity. D+L (**D**er Simonian and **L**aird method): pooled estimate of all studies. [b] The mixed linear regression models were adjusted for: age, age squared, height, sex, BMI, highest educational level, and smoking status at 2nd spirometry; negative estimates indicated lower lung function with increasing exposure.

Figure 3 and Figure 4

Forest plot displaying the study-specific mixed linear regression model estimates [a,b] of the association of NO_2 with level of FEV_1(in mL) **stratified by obesity status [c]**.



NO_2_1 indicates NO_2 measured at time of ESCAPE. [a] Associations with lung function measures are presented as increments in NO_2 per 10µg/m^3. I-square: variation in estimated effects attributable to heterogeneity. D+L (**D**er Simonian and **L**aird method): pooled estimate of all studies. [b] The mixed linear regression models were adjusted for: age, age squared, height, sex, BMI, highest educational level, and smoking status at 2nd spirometry; negative estimates indicated lower lung function with increasing exposure. [c] Obesity has been stratified as not obese "BMI<30 kg/m^2" and obese "BMI>=30 kg/m^2". P-value for heterogeneity obese vs. non-obese: 0.098 for FEV_1.