



CrossMark

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

Martin Adam^{1,2,27}, Tamara Schikowski^{1,2,3,27}, Anne Elie Carsin^{4,27}, Yutong Cai⁵, Benedicte Jacquemin^{4,6,7}, Margaux Sanchez^{6,7}, Andrea Vierkötter³, Alessandro Marcon⁸, Dirk Keidel^{1,2}, Dorothee Sugiri³, Zaina Al Kanani⁵, Rachel Nadif^{6,7}, Valérie Siroux^{9,10}, Rebecca Hardy¹¹, Diana Kuh¹¹, Thierry Rochat¹², Pierre-Olivier Bridevaux¹², Marloes Eeftens^{1,2,13}, Ming-Yi Tsai^{1,2}, Simona Villani¹⁴, Harish Chandra Phuleria^{1,2}, Matthias Birk¹⁵, Josef Cyrus^{15,16}, Marta Cirach⁴, Audrey de Nazelle¹⁷, Mark J. Nieuwenhuijsen⁴, Bertil Forsberg¹⁸, Kees de Hoogh⁵, Christophe Declercq¹⁹, Roberto Bono²⁰, Pavilio Piccioni²¹, Ulrich Quass²², Joachim Heinrich¹⁵, Deborah Jarvis^{5,23}, Isabelle Pin^{9,10,24}, Rob Beelen¹³, Gerard Hoek¹³, Bert Brunekreef^{13,25}, Christian Schindler^{1,2}, Jordi Sunyer^{4,28}, Ursula Krämer^{3,28}, Francine Kauffmann^{6,28}, Anna L. Hansell^{5,26,28}, Nino Künzli^{1,2,28} and Nicole Probst-Hensch^{1,2,28}

Affiliations: ¹Swiss Tropical and Public Health Institute, Basel. ²University of Basel, Basel, and ¹²Division of Pulmonary Medicine, University Hospitals of Geneva, Geneva, Switzerland. ³Leibniz Research Institute for Environmental Medicine (IUF), Düsseldorf, and ¹⁵Helmholtz Zentrum, München and German Research Centre for Environmental Health, Institute of Epidemiology I, Neuherberg. ¹⁶Environmental Science Center, University Augsburg, Augsburg, and ²²Air Quality and Sustainable Nanotechnology, IUTA Institut für Energie- und Umwelttechnik e.V., Duisburg, Germany. ⁴Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain. ⁵MRC-PHE Centre for Environment and Health, Dept of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, ¹¹MRC University Unit for Lifelong Health and Ageing, University College London, London, ¹⁷Centre for Environmental Policy, Imperial College London, London, ²³Dept of Respiratory Epidemiology and Public Health, National Heart and Lung Institute, Imperial College London, London, and ²⁶Public Health and Primary Care Directorate, Imperial College Healthcare NHS Trust, London, UK. ⁶Inserm, Centre for Research in Epidemiology and Population Health (CESP), U1018, Respiratory and Environmental Epidemiology Team, Villejuif. ⁷Univ. Paris-Sud, UMRS 1018, Villejuif, ⁹Inserm U823, Environmental Epidemiology Applied to Reproduction and Respiratory Health Team, Grenoble. ¹⁰Univ. Joseph Fourier, Grenoble, ¹⁹French Institute for Public Health Surveillance, Saint-Maurice, and ²⁴Pédiatrie, CHU de Grenoble, La Tronche, France. ⁸Unit of Epidemiology and Medical Statistics, Dept of Public Health and Community Medicine, University of Verona, Verona. ¹⁴Unit of Biostatistics and Clinical Epidemiology Dept of Public Health, Experimental and Forensic Medicine University of Pavia, Pavia. ²⁰Dept of Public Health and Pediatrics, University of Turin, Turin, and ²¹SC Pneumologia CPA ASL 4 Turin, Turin, Italy. ¹³Institute for Risk Assessment Sciences, Utrecht University, Utrecht, and ²⁵Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. ¹⁸Environmental and Occupational Medicine, Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. ²⁷These authors contributed equally. ²⁸Steering Committee of ESCAPE Work Package 4 on Respiratory Health in Adults.

Correspondence: Nicole Probst-Hensch, Head Unit Chronic Disease Epidemiology, Swiss Tropical and Public Health Institute, Socinstrasse 57, P.O. Box, 4002 Basel, Switzerland. E-mail: Nicole.Probst@unibas.ch

ABSTRACT The chronic impact of ambient air pollutants on lung function in adults is not fully understood. The objective of this study was to investigate the association of long-term exposure to ambient air pollution with lung function in adult participants from five cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE).

Residential exposure to nitrogen oxides (NO₂, NO_x) and particulate matter (PM) was modelled and traffic indicators were assessed in a standardised manner. The spirometric parameters forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) from 7613 subjects were considered as outcomes. Cohort-specific results were combined using meta-analysis.

We did not observe an association of air pollution with longitudinal change in lung function, but we observed that a 10 µg·m⁻³ increase in NO₂ exposure was associated with lower levels of FEV₁ (−14.0 mL, 95% CI −25.8 to −2.1) and FVC (−14.9 mL, 95% CI −28.7 to −1.1). An increase of 10 µg·m⁻³ in PM₁₀, but not other PM metrics (PM_{2.5}, coarse fraction of PM, PM absorbance), was associated with a lower level of FEV₁ (−44.6 mL, 95% CI −85.4 to −3.8) and FVC (−59.0 mL, 95% CI −112.3 to −5.6). The associations were particularly strong in obese persons.

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.



@ERSpublications

The ESCAPE study finds that, even at very low levels, air pollution has adverse effects on lung function in adults <http://ow.ly/A1ssB>

Introduction

Lung function, specifically forced vital capacity (FVC) and forced expiratory volume in 1 s (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 of the predominantly cross-sectional studies [4–7], FORBES *et al.* [4] found increases in 10 µg·m⁻³ of particulate matter of size 10 µm or less (PM₁₀) associated with a decrease of about 3% in FEV₁. At first spirometry SAPALDIA found an increase of 10 µg·m⁻³ in annual mean concentration of PM₁₀ was associated with 3.4% lower FVC and 1.6% lower FEV₁ [5]. The SALIA study of females showed negative associations of PM₁₀ concentrations with FEV₁ and FVC (5.1% and 3.7% respectively, per 7 µg·m⁻³ 5-year annual mean PM₁₀) [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 PM₁₀ exposure over a period of 11 years attenuated the age-related decrease in respiratory function [8]. A more recent study found cumulative long-term exposure to ambient PM₁₀ and ozone associated with both FEV₁ and FVC decline in an elderly population and suggested an increased susceptibility among frail persons [9]. Statistically significant associations were also reported for NO₂ and traffic exposure [5, 7].

The ESCAPE project (European Study of Cohorts for Air Pollution Effects) combined data from over 30 cohort studies and modelled home outdoor levels of air pollution in a standardised 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 five European cohorts/studies from eight countries with information on lung function and the most important potential confounders. The analyses were based on subpopulations from the 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) (online supplementary material (methods: cohorts section) and supplementary table S1). Criteria for inclusion of cohort participants in the present analyses were: age of at least 20 years; pre-bronchodilation spirometry data from two different time points approximately one decade apart (referred to as first and second 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 NO₂/NO_x/traffic indicators (referred to as NO-population) and PM metrics (a subsample of the NO population, referred to as PM-population). Of 13 259 participants with first and second spirometry living in ESCAPE monitoring

For editorial comments see *Eur Respir J* 2015; 45: 11–13 [DOI: 10.1183/09031936.00168814].

This article has online supplementary material available from erj.ersjournals.com

Received: July 16 2014 | Accepted after revision: July 24 2014 | First published online: Sept 05 2014

Support statement: The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007–2011) under grant agreement number 211250. Funding details for the individual study cohorts of the ESCAPE project (ECRHS/ECRHS II, EGEA, NHSD, SALIA and SAPALDIA) can be found in the acknowledgements section. 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.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Copyright ©ERS 2015. ERJ Open articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

areas, 7615 and 4233, respectively provided complete datasets towards analysis of NO₂/NO_x/traffic indicators and PM metrics (supplementary figure S1). 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.

Exposure data

ESCAPE exposure assessment has been described previously, and is based on fully standardised measurement and modelling protocols (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 and 2011 measured NO₂ and NO_x as well as, in a smaller number of areas PM_{2.5}, PM₁₀, the coarse fraction of PM (PM₁₀ minus PM_{2.5}) and light absorbance of PM_{2.5}. Within each study area, concentration levels were monitored at 40 (NO₂, 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-m buffer of the home. Traffic measures were often used in other studies as proxies of exposure to near-road pollutants, such as 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; supplementary table S2), sensitivity analyses replaced ESCAPE exposure estimates with estimates back extrapolated to the time of first and second spirometry (except for the time of first spirometry in ECRHS and EGEA, where no historical data was available, and of second spirometry in NSHD and SALIA conducted between 2006 and 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 (NO₂ and PM₁₀ only). For each study participant's home address the back extrapolated concentration was obtained by multiplying the modelled 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 (details can be found in www.escapeproject.eu/manuals/) [12]. The procedures applied assumed that the within-city spatial contrasts remained proportional over time. GULLIVER *et al.* [15] confirmed the validity of this assumption for the UK.

Lung function metrics and outcomes

FEV₁ and FVC were used as outcome metrics. In cross-sectional analysis, we focused on lung function measured at the second spirometry (time point closest to ESCAPE air pollution monitoring). Change in lung function between first and second spirometry was assessed as both annual lung function change (mL·year⁻¹) and annual change in lung function as a percentage of the first spirometry value (%·year⁻¹) (supplementary material; methods: lung function metrics and outcomes section), 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

First, study specific data were analysed 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 modelling. 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 standardised across studies (supplementary material; methods section). In the absence of materially different effect estimates derived from models adjusting for additional covariates, we chose as main

analytical model the one adjusting for age (years), age squared, height (cm), sex, body mass index (BMI; $\text{kg}\cdot\text{m}^{-2}$), educational level (low as reference, medium, high), and smoking status (never as reference, ever). Models analysing 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 cut-off for dichotomising the continuous traffic exposure (≤ 5000 and > 5000 cars per day for traffic intensity on the nearest major road; ≤ 500 and > 500 car-km driven per day for the traffic intensity on major roads in a 100 m buffer) (supplementary material; methods: statistic models section). Traffic variables were also analysed 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-analysed (supplementary material; methods: meta-analysis section).

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 *versus* males; not obese *versus* obese; never *versus* ever smokers; never asthma *versus* ever asthma) using a chi-square test with one degree of freedom. In sensitivity analyses we restricted the analytical model to non-movers and participants aged ≥ 30 years (age at first spirometry).

A standardised analytical approach was used to minimise the possibility of differential bias across participating cohorts. We controlled for different known or potential individual confounding factors in our analyses. Moreover, we included random effects for the different cohort areas to adjust for geographic clustering of outcomes. Additionally, we performed several sensitivity analyses in selected subsamples to address specific potential biases (e.g. in the subsample of non-movers to address potential bias due to health-related changes in exposure).

Statistical analyses were performed using STATA, version 12 (Stata Statistical Software, Release 12; StataCorp., College Station, TX, USA).

Results

Study characteristics

Table 1 provides a description of the cohort specific study populations. The average age of the cohorts at the time of second spirometry ranged from 43 years (ECRHS) to 73 years (SALIA). The SALIA population, consisting exclusively of females, exhibited the lowest mean levels of FEV₁ (2.20 L) and FVC (2.91 L) (table 1) (for the smaller PM subpopulation and for the cohort-specific lung function distributions stratified by sex, smoking and asthma status, refer to supplementary table S3).

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 PM₁₀ (supplementary table S4). 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 (supplementary table S5). The study specific correlations between the exposure metrics were generally highest between NO_2 and NO_x (ρ of 0.90–0.98), but moderate to low between pollutants and traffic indicators (supplementary table S6). ESCAPE derived exposures were highly correlated with the exposures back-extrapolated to the time of the second spirometry ($\rho(\text{NO}_2) \geq 0.94$; $\rho(\text{PM}_{10}) \geq 0.91$), but less strongly correlated with exposures back-extrapolated to the first spirometry ($0.56 \leq \rho(\text{NO}_2) \leq 0.92$; $0.47 \leq \rho(\text{PM}_{10}) \leq 0.74$).

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 (sex, obesity, asthma and 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 FEV₁. An increase of $10 \mu\text{g}\cdot\text{m}^{-3}$ in NO_2 exposure was associated with a -14.0 mL lower level of FEV₁ (95% CI -25.8 – -2.1) and -14.9 mL lower level of FVC (95% CI -28.7 – -1.1) (table 3, figs 1 and 2). An increase of $20 \mu\text{g}\cdot\text{m}^{-3}$ in NO_x exposure was associated with a lower level of FEV₁, by -12.9 mL (95% CI -23.87 – -2.0) and of FVC, by -13.3 mL (95% CI -25.9 – -0.7) and an increase of $10 \mu\text{g}\cdot\text{m}^{-3}$ in PM₁₀ was associated with a lower level of FEV₁ (-44.6 mL, 95% CI -85.4 – -3.8) and FVC (-59.0 mL, 95% CI -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 100 m buffer from residential address was associated with lower levels of FEV₁ (-32.34 mL, 95% CI -59.30 – -5.38).

TABLE 1 Description of cohort-specific study populations

	ECRHS	EGEA	NSHD	SALIA	SAPALDIA
Total n	3859	568	844	580	1764
First spirometry	1991–1993	1991–1995	1999	1985–1994	1991–1992
Second spirometry	2001–2002	2003–2007	2006–2010	2007–2009	2002
Female	1981 (51.3)	303 (53.3)	471 (55.8)	580 (100.0)	980 (55.6)
Age years	43.0±7.2	53.1±11.3	63.3±1.1	73.3±3.4	53.2±11.0
BMI kg·m⁻²	25.7±4.6	25.3±4.3	27.7±4.9	27.4±4.5	25.4±4.3
Height cm	168.6±9.5	168.5±8.4	167.4±8.6	162.3±5.5	168.8±9.0
Ex-smoker	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 first spirometry[#]	7.7±12.0	5.9±10.0	9.1±12.6	2.8±8.4	10.9±17.9
Pack years from first to second spirometry[#]	3.9±10.9	1.7±8.3	0.7±2.5	0.6±6.7	3.1±6.5
Medium educational level[#]	1321 (34.2)	118 (20.8)	439 (52.0)	276 (47.6)	1121 (63.5)
High educational level[#]	1420 (36.8)	263 (46.3)	102 (12.1)	199 (34.3)	520 (29.5)
Environmental tobacco exposure at home or at work[#]	676 (17.5)	233 (41.0)	168 (19.9)	347 (59.8)	119 (6.7)
Occupational exposure to dust/fumes or gases[#]	1685 (43.7)	125 (22.0)	246 (29.1)	39 (6.7)	460 (26.1)
Ever asthma^{#,¶}	616 (16.0)	183 (32.2)	83 (9.8)	50 (8.6)	155 (8.8)
FEV₁ 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±1.00	4.00±1.01	3.57±0.81	2.91±0.54	4.08±1.02
FEV₁ change⁺ L	-0.026±0.032	-0.028±0.031	-0.022±0.025	-0.020±0.014	-0.033±0.030
FVC change⁺ L	-0.018±0.040	-0.015±0.037	-0.025±0.034	-0.022±0.019	-0.022±0.041

Data are presented as mean±SD for continuous variables, or n (%) for categorical variables, unless otherwise stated. Characteristics refer to time point of second spirometry, and are presented for the larger subgroup of participants included in the analysis of NO₂ and NO_x and traffic indicators (characteristics for the smaller subgroup of participants included in the particulate matter metrics analyses are presented in supplementary table S1). BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: information missing on a limited number of subjects; [¶]: asthma diagnosed by a physician at first and/or at second spirometry; ⁺: change in lung function between first and second spirometry.

TABLE 2 Distribution of all exposure estimates (annual averages of ambient air pollutants and traffic indicators), at participants residential addresses in each cohort

Exposures	ECRHS			EGEA			NSHD			SALIA			SAPALDIA		
	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_{2.5} absorbance ×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
PM₁₀ 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
Coarse PM[#] 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
NO₂ 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[¶]	2492	4807	5509	568	6633	6667	844	1239	0	580	1642	0	1697	3207	3876
Traffic load on nearest major road⁺	2687	1.45	1.67	568	1.37	1.58	844	0.27	0	580	0.72	0.32	1671	0.94	1.42
NO₂ back-extrapolated to first spirometry µg·m⁻³	NA [§]	NA [§]	NA [§]	NA [§]	NA [§]	NA [§]	841	26.3	11.2	580	36.0	14.0	1762	47.7	12.3
PM₁₀ back-extrapolated to first spirometry µg·m⁻³	NA [§]	NA [§]	NA [§]	NA [§]	NA [§]	NA [§]	748	22.0	2.6	580	47.7	13.6	726	46.2	4.0
NO₂ back-extrapolated to second spirometry µg·m⁻³	3859	34.2	23.0	568	32.1	17.5	NA ^f	NA ^f	NA ^f	NA ^f	NA ^f	NA ^f	1764	31.0	8.0
PM₁₀ back-extrapolated to second spirometry µg·m⁻³	1388	27.1	8.4	148	27.0	5.3	NA ^f	NA ^f	NA ^f	NA ^f	NA ^f	NA ^f	729	37.8	4.3

IQR: interquartile range; PM_{2.5}: particulate matter with a diameter of ≤2.5 µm; PM₁₀: particulate matter with a diameter of ≤10 µm. [#]: fraction of PM_{2.5} to relative to PM₁₀; [¶]: cars per day; ⁺: traffic load on nearest major road within a 100 m buffer presented in thousands of car-km driven per day; [§]: no complete exposure back-extrapolation to first spirometry available; ^f: no back-extrapolation applied as time point of second spirometry coincides with time point of ESCAPE monitoring campaign.

Associations observed for NO₂ and PM₁₀ with FEV₁ and FVC at second spirometry remained largely unaltered when ESCAPE exposure estimates of NO₂ and PM₁₀ in ECRHS, EGEA and SAPALDIA were replaced with NO₂ and PM₁₀ estimates back-extrapolated to the time point of the second spirometry. The inverse association between PM₁₀ and FVC became stronger and statistically significant (supplementary table S7).

In subgroup analysis, the NO₂ and NO_x (data not shown) associations with FEV₁ and FVC were particularly observed in obese participants (FEV₁: figures 3 and 4; FVC: supplementary figures S2 and S3) (p-values for heterogeneity, obese *versus* non-obese: p=0.098 for NO₂/FEV₁ (figures 3 and 4); p=0.026 for NO₂/FVC (supplementary figures S2 and S3); p=0.050 for NO_x/FVC). All other tested factors (sex, smoking and asthma status) showed no or only weak evidence for modification of the air pollution lung function associations (NO₂: supplementary table S8). The effect modification by obesity was also evident in sex-stratified analyses, with substantially stronger inverse NO₂ and NO_x associations with FEV₁ and FVC, in both obese females and males (NO₂: supplementary table S9).

In sensitivity analysis, looking at non-movers and participants aged 30 years or more, we did not find a particular difference from the observed main associations (supplementary table S10).

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 standardised across different cities and regions in Europe. Impaired lung function characterised by reduced FEV₁, 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 and PM₁₀, as well as to 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 (supplementary table S6) 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 limited number of centres. NO₂, which characterises the spatial variation of traffic related air pollution, has been linked with stronger lung function impairment depending on the parameter studied, but evidence that PM effects are 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 calibre 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 subjects [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 FEV₁ and FVC decline.

Strengths and weaknesses

Our study benefits from a large number of observations, and the multicentre design across different European regions, covering 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.

TABLE 3 Results of meta-analyses for the association between level and change of lung function and exposure to air pollution and traffic intensity indicators

Exposure (increment)	Level of lung function (mL) [#]					
	FEV1			FVC		
	Beta [¶]	95% CI	I ² § p-value (het)	Beta [¶]	95% CI	I ² § p-value (het)
NO ₂ (10 µg·m ⁻³)	-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·m ⁻³)	-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·m ⁻³)	-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·m ⁻³)	-21.14	-56.37 to 14.08	0.0% p=0.535	-36.39	-83.29 to 10.50	0.0% p=0.877
PM _{2.5} absorbance (1×10 ⁻⁵ m ⁻¹)	-24.40	-55.58 to 6.79	0.0% p=0.709	-12.94	-50.23 to 24.30	0.0% p=0.619
Coarse PM (5 µg·m ⁻³)	-22.36	-94.00 to 49.27	12.6% p=0.333	2.88	-87.85 to 93.60	0.0% p=0.760
Traffic intensity on nearest road (high/low) ^{f,##}	-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 100-m buffer (high/low) ^{##,¶¶}	-32.34	-59.30 to -5.38	0.0% p=0.784	-18.64	-50.22 to 12.94	0.0% p=0.967

Exposure (increment)	Change in lung function (mL per year)					
	FEV1			FVC		
	Beta ^{§§}	95% CI	I ² § p-value (het)	Beta ^{§§}	95% CI	I ² § p-value (het)
NO ₂ (10 µg·m ⁻³)	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·m ⁻³)	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·m ⁻³)	-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·m ⁻³)	-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 _{2.5} absorbance (1×10 ⁻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
Coarse PM (5 µg·m ⁻³)	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 (high/low) ^{f,##}	-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 100-m buffer (high/low) ^{##,¶¶}	-0.32	-1.81 to 1.18	0.0% p=0.987	0.34	-1.56 to 2.25	0.0% p=0.672

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PM: particulate matter. [#]: level of lung function for cross-sectional analysis was derived from second spirometry. [¶]: the beta values for the association between level of lung function and exposure are adjusted for age, age squared, height, sex, body mass index (BMI), highest educational level, and smoking status at second spirometry; a negative sign indicates lower lung function with increasing exposure. [§]: I² and Cochran's test for heterogeneity of effect estimates between cohorts. ^f: low traffic intensity on nearest road: ≤5000 cars per day; high: >5000 cars per day. ^{##}: associations with traffic intensity (high/low) and traffic load (high/low) were additionally adjusted for background NO₂ concentrations. ^{¶¶}: low traffic load on the nearest major road in a 100-m buffer: ≤500 car-km driven per day; high: >500 car-km driven per day. ^{§§}: the beta values of the association between change in lung function and exposure are adjusted for sex, age and height at first spirometry, highest educational level, smoking at first spirometry, smoking cessation and change in BMI to the second spirometry; a negative sign indicates steeper lung function decline with increasing exposure.

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

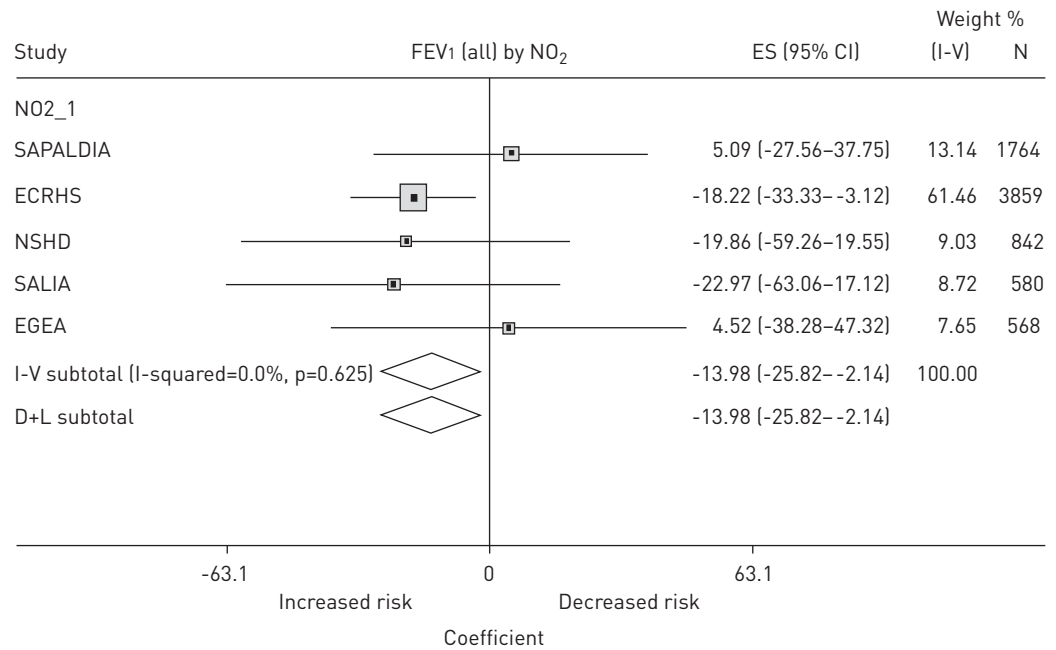


FIGURE 1 Forest plot displaying the study-specific mixed linear regression model estimates of the association of NO₂ with level of forced expiratory volume in 1 s (FEV₁; in mL) (based on all study participants living in sites with ESCAPE models available). NO_{2_1} indicates NO₂ measured at time of ESCAPE. Associations with lung function measures are presented as increments in NO₂ per 10 µg·m⁻³. I-square: variation in estimated effects attributable to heterogeneity. D+L (Der Simonian and Laird method): pooled estimate of all studies. The mixed linear regression models were adjusted for: age, age squared, height, sex, body mass index, highest educational level, and smoking status at second spirometry; negative estimates indicated lower lung function with increasing exposure. ES: effect size.

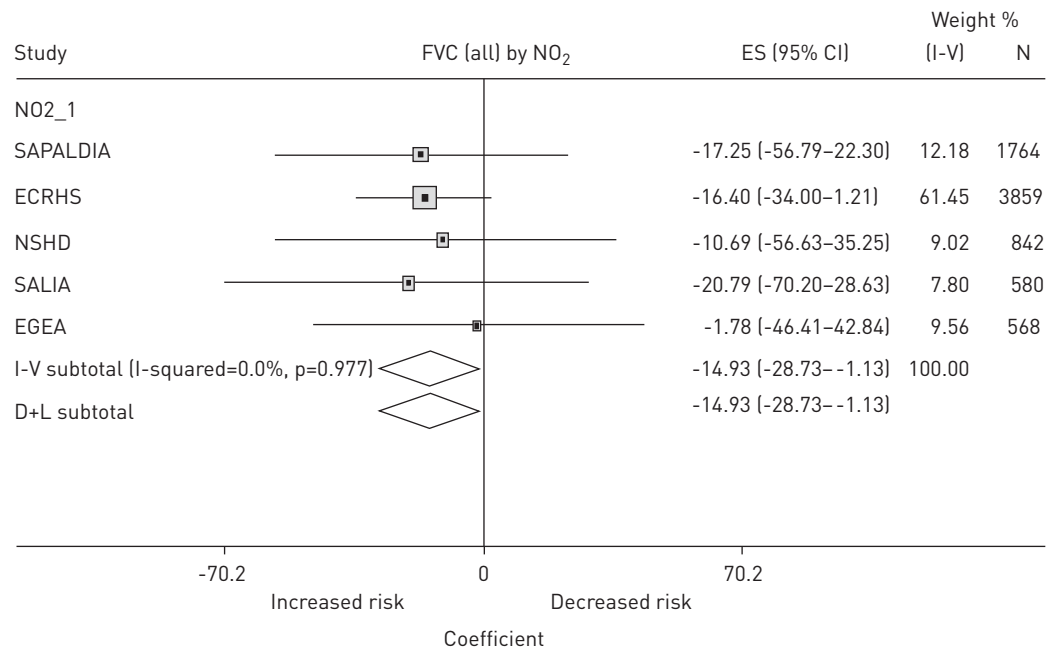


FIGURE 2 Forest plot displaying the study-specific mixed linear regression model estimates of the association of NO₂ with level of forced vital capacity FVC; in mL) (based on all study participants living in sites with ESCAPE models available). NO_{2_1} indicates NO₂ measured at time of ESCAPE. Associations with lung function measures are presented as increments in NO₂ per 10 µg·m⁻³. I-square: variation in estimated effects attributable to heterogeneity. D+L (Der Simonian and Laird method): pooled estimate of all studies. The mixed linear regression models were adjusted for: age, age squared, height, sex, body mass index, highest educational level, and smoking status at second spirometry; negative estimates indicated lower lung function with increasing exposure. ES: effect size.

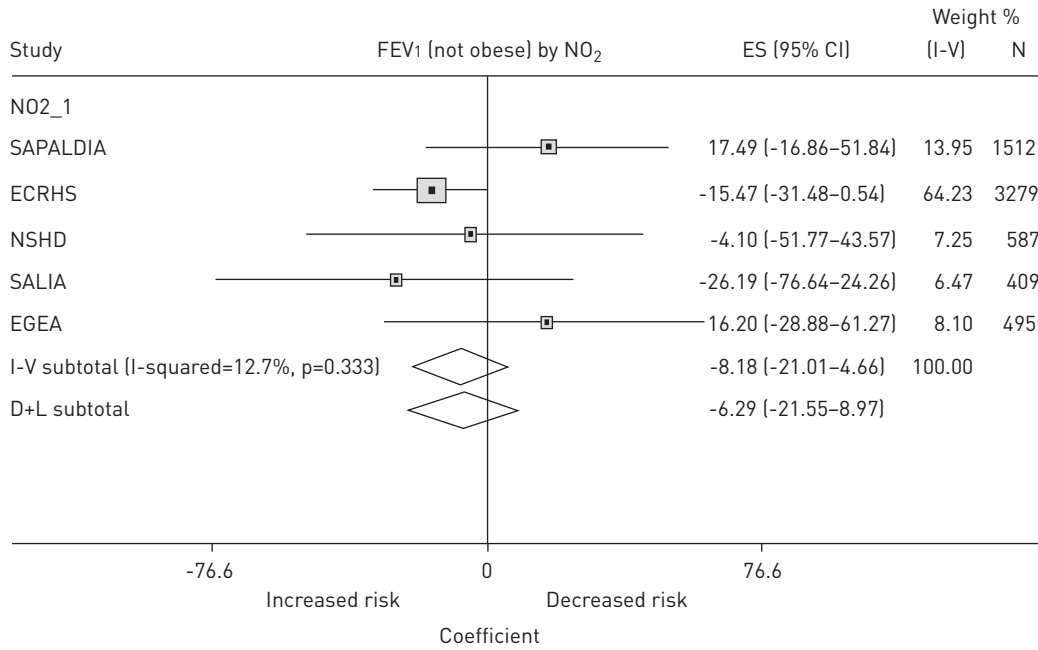


FIGURE 3 Forest plot displaying the study-specific mixed linear regression model estimates of the association of NO₂ with level of forced expiratory volume in 1 s (FEV₁; in mL) in participants stratified as not obese (body mass index (BMI) <30 kg·m⁻²). NO₂_1 indicates NO₂ measured at time of ESCAPE. Associations with lung function measures are presented as increments in NO₂ per 10 µg·m⁻³. I-square: variation in estimated effects attributable to heterogeneity. D+L (Der Simonian and Laird method): pooled estimate of all studies. The mixed linear regression models were adjusted for: age, age squared, height, sex, BMI, highest educational level, and smoking status at second spirometry; negative estimates indicated lower lung function with increasing exposure. p-value for heterogeneity, obese *versus* non-obese: 0.098 for FEV₁. ES: effect size.

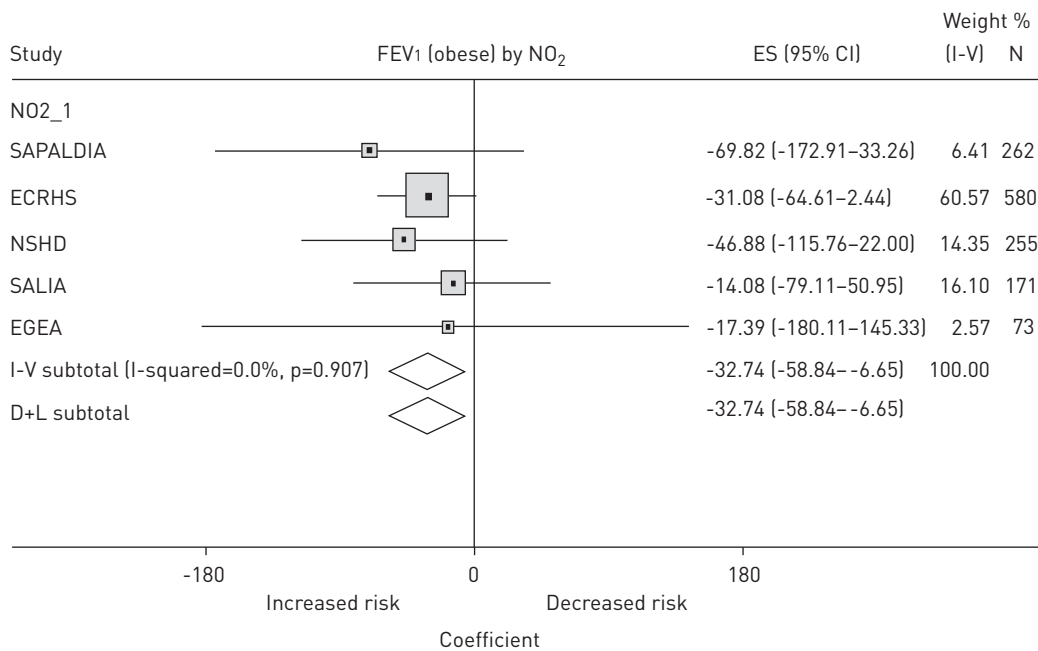


FIGURE 4 Forest plot displaying the study-specific mixed linear regression model estimates of the association of NO₂ with level of forced expiratory volume in 1 s (FEV₁; in mL) in obese participants (body mass index (BMI) ≥30 kg·m⁻²). NO₂_1 indicates NO₂ measured at time of ESCAPE. Associations with lung function measures are presented as increments in NO₂ per 10 µg·m⁻³. I-square: variation in estimated effects attributable to heterogeneity. D+L (Der Simonian and Laird method): pooled estimate of all studies. The mixed linear regression models were adjusted for: age, age squared, height, sex, BMI, highest educational level, and smoking status at second spirometry; negative estimates indicated lower lung function with increasing exposure. p-value for heterogeneity, obese *versus* non-obese: 0.098 for FEV₁. ES: effect size.

also amplified in the longitudinal analyses. Most importantly, back-extrapolation of residential pollution levels is of prime relevance to properly characterise exposure at first 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 LURs 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 unrecognised effect modification. The associations were not sensitive to the SALIA study consisting exclusively of females and exhibiting the lowest mean levels of lung function (supplementary figures S4 and S5 for associations of NO₂ with FEV₁ and FVC in females). Non-participation at follow-up of subjects with low lung function may bias observed associations or limit their generalisability. In SAPALDIA, subjects with better lung function were more likely to participate in the second 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.

Acknowledgements

We acknowledge the support of an external advisory board consisting of Mike Jerrett (UC Berkeley, Berkeley, CA, USA), Joel Kaufman (University of Washington, Seattle, WA, USA), Ross Anderson (King's College London, London, UK), Michal Krzyzanowski (World Health Organization, Bonn, Germany), Aaron Cohen (Health Effects Institute, Boston, MA, USA).

We thank all study members and staff involved in data collections in each cohort and also the respective funding bodies for ECRHS, EGEE, NSHD, SALIA and SAPALDIA.

ECRHS

The ECRHS data incorporated in this analysis would not have been available without the collaboration of the following individuals and their research teams.

ECRHS co-ordinating centre: P. Burney, D. Jarvis, S. Chinn, J. Knox (ECRHS II), C. Luczynska[†], J. Potts.

Steering Committee for ECRHS II: P. Burney, D. Jarvis, S. Chinn, J.M. Anto, I. Cerveri, R. deMarco, T. Gislason, J. Heinrich, C. Janson, N. Kunzli, B. Leynaert, F. Neukirch, T. Rochat, J. Schouten, J. Sunyer, C. Svanes, P. Vermeire[†], M. Wjst.

Principal Investigators and Senior Scientific Teams for ECRHS II: Australia: Melbourne (M. Abramson, R. Woods, E.H. Walters, F. Thien); Belgium: South Antwerp and Antwerp City (P. Vermeire[†], J. Weyler, M. Van Sprundel, V. Nelen); Denmark: Aarhus (E.J. Jensen); Estonia: Tartu (R. Jogi, A. Soon); France: Paris (F. Neukirch, B. Leynaert, R. Liard, M. Zureik), Grenoble (I. Pin, J. Ferran-Quentin), Bordeaux (A. Taytard, C. Raherison), Montpellier (J. Bousquet, P. Demoly); Germany: Erfurt (J. Heinrich, M. Wjst, C. Frye, I. Meyer), Hamburg (K. Richter); Iceland: Reykjavik (T. Gislason, E. Bjornsson, D. Gislason, T. Blondal, A. Karlsdottir); Italy: Turin (M. Bugiani, P. Piccioni, E. Caria, A. Carosso, E. Migliore, G. Castiglioni), Verona (R. de Marco, G. Verlato, E. Zanolin, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari), Pavia (A. Marinoni, S. Villani, M. Ponzio, F. Frigerio, M. Comelli, M. Grassi, I. Cerveri, A. Corsico); the Netherlands: Groningen and Geleen (J. Schouten, M. Kerkhof); Norway: Bergen (A. Gulsvik, E. Omenaas, C. Svanes, B. Laerum); Spain: Barcelona (J.M. Anto, J. Sunyer, M. Kogevinas, J.P. Zock, X. Basagana, A. Jaen, F. Burgos), Huelva (J. Maldonado, A. Pereira, J.L. Sanchez), Albacete (J. Martinez-Moratalla Rovira, E. Almar), Galdakao (N. Muniozgueren, I. Urritia), Oviedo (F. Payo); Sweden: Uppsala (C. Janson, G. Boman, D. Norback, M. Gunnbjornsdottir), Goteborg (K. Toren, L. Lillienberg, A.C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg), Umea (E. Norrman, M. Soderberg, K. Franklin, B. Lundback, B. Forsberg, L. Nystrom); Switzerland: Basel (N. Kunzli, B. Dibbert, M. Hazenkamp, M. Brutsche, U. Ackermann-Liebrich); UK: Norwich (D. Jarvis, B. Harrison), Ipswich (D. Jarvis, R. Hall, D. Seaton); USA: Portland (M. Osborne, S. Buist, W. Vollmer, L. Johnson).

The excellent fieldwork by Gabriele Wölke and Matthias Birk is highly acknowledged.

EGEE

Coordination: V. Siroux (epidemiology, PI since 2013), F. Demenais (genetics), I. Pin (clinical aspects), R. Nadif (biology), F. Kauffmann (PI 1992–2012).

Respiratory epidemiology: Inserm U 700, Paris: M. Korobaëff (Egea1), F. Neukirch (Egea1); Inserm U 707, Paris: I. Annesi-Maesano (Egea1-2); Inserm CESP/U 1018, Villejuif: F. Kauffmann, N. Le Moual, R. Nadif, M.P. Oryszczyn (Egea1-2), R. Varraso; Inserm U 823, Grenoble: V. Siroux.

Genetics: Inserm U 393, Paris: J. Feingold; Inserm U 946, Paris: E. Bouzigon, F. Demenais, M.H. Dizier; CNG, Evry: I. Gut (now CNAG, Barcelona, Spain), M. Lathrop (now Univ. McGill, Montreal, Canada).

Clinical centres: Grenoble: I. Pin, C. Pison; Lyon: D. Ecochard (Egea1), F. Gormand, Y. Pacheco; Marseille: D. Charpin (Egea1), D. Vervloet (Egea1-2); Montpellier: J. Bousquet; Paris Cochin: A. Lockhart (Egea1), R. Matran (now in Lille); Paris Necker: E. Paty (Egea1-2), P. Scheinmann (Egea1-2); Paris-Trousseau: A. Grimfeld (Egea1-2), J. Just.

Data and quality management: Inserm ex-U155 (Egea1): J. Hochez; Inserm CESP/U 1018, Villejuif: N. Le Moual; Inserm ex-U780: C. Ravault (Egea1-2); Inserm ex-U794: N. Chateigner (Egea1-2); Grenoble: J. Quentin-Ferran (Egea1-2).

NHSD

We acknowledge the NSHD participants and the NSHD scientific and data collection teams.

SALIA

Over the past decades, many scientists, study nurses and laboratories were involved in conducting the study. As representatives for all these people we would like to thank especially Reinhard Dolgner (MD) for organising the baseline study and Barbara Schulten as study nurse for her help in organising the follow-up study. We are most grateful for all the females from the Ruhr area and from Borken who participated in the study over the decades.

SAPALDIA

Study directorate: T. Rochat (pneumology), N.M. Probst Hensch (epidemiology/genetic and molecular biology), J.M. Gaspoz (cardiology), N. Künzli (epidemiology/exposure), C. Schindler (statistics).

Scientific team: J.C. Barthélémy (cardiology), W. Berger (genetic and molecular biology), R. Bettschart (pneumology), A. Bircher (allergology), G. Bolognini (pneumology), O. Brändli (pneumology), C. Brombach (nutrition), M. Brutsche (pneumology), L. Burdet (pneumology), M. Frey (pneumology), U. Frey (paediatrics), M.W. Gerbase (pneumology), D. Gold (epidemiology / cardiology / pneumology), E. de Groot (cardiology), W. Karrer (pneumology), R. Keller (pneumology), B. Knöpfli (pneumology), B. Martin (physical activity), D. Miedinger (occupational health), U. Neu (exposure), L. Nicod (pneumology), M. Pons (pneumology), F. Roche (cardiology), T. Rothe (pneumology), E. Russi (pneumology), P. Schmid-Grendelmeyer (allergology), A. Schmidt-Trucksäss (physical activity), A. Turk (pneumology), J. Schwartz (epidemiology), D. Stolz (pneumology), P. Straehl (exposure), J.M. Tschopp (pneumology), A. von Eckardstein (clinical chemistry), E. Zemp Stutz (epidemiology).

Scientific team at coordinating centres: M. Adam (epidemiology/genetic and molecular biology), E. Boes (genetic and molecular biology), P.O. Bridevaux (pneumology), D. Carballo (cardiology), E. Corradi (epidemiology), I. Curjuri (epidemiology), J. Dratva (epidemiology), A. Di Pasquale (statistics), L. Grize (statistics), D. Keidel (statistics), S. Kriemler (physical activity), A. Kumar (genetic and molecular biology), M. Imboden (genetic and molecular biology), N. Maire (statistics), A. Mehta (epidemiology), F. Meier (epidemiology), H. Phuleria (exposure), E. Schaffner (statistics), G.A. Thun (genetic and molecular biology), A. Ineichen (exposure), M. Ragetti (epidemiology), M. Ritter (exposure), T. Schikowski (epidemiology), G. Stern (paediatrics), M. Tarantino (statistics), M. Tsai (epidemiology), M. Wanner (physical activity).

The study could not have been done without the help of the study participants, technical and administrative support and the medical teams and field workers at the local study sites.

Local fieldworkers: Aarau: S. Brun, G. Giger, M. Sperisen, M. Stahel; Basel: C. Bürli, C. Dahler, N. Oertli, I. Harreh, F. Karrer, G. Novicic, N. Wyttenbacher; Davos: A. Saner, P. Senn, R. Winzeler; Geneva: F. Bonfils, B. Blicharz, C. Landolt, J. Rochat; Lugano: S. Boccia, E. Gehrig, M.T. Mandia, G. Solari, B. Viscardi; Montana: A.P. Bieri, C. Darioly, M. Maire; Payerne: F. Ding, P. Danieli A. Vonnez; Wald: D. Bodmer, E. Hochstrasser, R. Kunz, C. Meier, J. Rakic, U. Schafroth, A. Walder.

Administrative staff: C. Gabriel, R. Gutknecht.

The authors wish to acknowledge the funding provided to the individual study cohorts as follows.

ECRHS was supported by the European Commission, as part of their Quality of Life program. The coordination of ECRHS II was supported by the European Commission, as part of their Quality of Life programme. The following bodies funded the local studies in ECRHS II in this article: Albacete-Fondo de Investigaciones Santarias (grant code: 97/0035-01, 13 99/0034-01, and 99/0034-02) (Hospital Universitario de Albacete, Consejería de Sanidad); Antwerp-FWO (Fund for Scientific Research), Flanders, Belgium (grant code: G.0402.00) (University of Antwerp, Flemish Health Ministry); Barcelona-Fondo de Investigaciones Sanitarias (grant code: 99/0034-01, and 99/0034-02), Red Respira (RTIC 03/11 ISC IIF); Ciber de Epidemiology and Public Health was established and founded by Instituto de Salud Carlos III; Erfurt-GSF-National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (DFG) (grant code FR 1526/1-1); Galdakao-Basque Health Department; Grenoble-Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 no.2610, Ministry of Health, Direction de la Recherche Clinique, Ministère de l'Emploi et de la Solidarite, Direction Generale de la Sante, CHU de Grenoble, Comite des Maladies Respiratoires de l'Isere; Ipswich and Norwich-National Asthma Campaign (UK); Huelva-Fondo de Investigaciones Sanitarias (FIS) (grant code: 97/0035-01, 99/0034-01, and 99/0034-02); Oviedo-Fondo de Investigaciones Santarias (FIS) (grant code: 97/0035-01, 99/0034-01, and 99/0034-02); Paris-Ministere de l'Emploi et de la Solidarite, Direction Generale de la Sante, UCBPharma (France), Aventis (France), Glaxo France, Programme Hospitalier de Recherche Clinique-DRC de Grenoble 2000 no. 2610, Ministry of Health, Direction de la Recherche Clinique, CHU de Grenoble; measurements and models for PM in

Grenoble (ECRHS) were funded by Region Rhône-Alpes; Pavia-Glaxo, Smith and Kline Italy, Italian Ministry of University and Scientific and Technological Research (MURST), Local University Funding for Research 1998 and 1999 (Pavia, Italy); Turin-ASL 4 Regione Piemonte (Italy), AO CTO/ICORMA Regione Piemonte (Italy), Ministero dell'Università e della Ricerca Scientifica (Italy), Glaxo Wellcome spa (Verona, Italy); Umeå-Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences and Allergy Research, Swedish Asthma and Allergy Foundation, Swedish Cancer and Allergy Foundation; Verona-University of Verona; Italian Ministry of University and Scientific and Technological Research (MURST); Glaxo, Smith and Kline Italy.

EGEA is funded in part by PHRC-Paris, PHRC-Grenoble, ANR 05-SEST-020-02/05-9-97, ANR-06-CEBS, ANRCES-2009, Région Nord Pas-de-Calais, Merck Sharp and Dohme (MSD).

NSHD and Profs R. Hardy and D. Kuh are supported by core funding and grant funding (U1200632239 and U12309272) from the UK Medical Research Council. The authors acknowledge the NSHD participants and the NSHD scientific and data collection teams.

SALIA received funds from the German state (NRW) and federal Ministries of the Environment. The follow-up investigation was funded by the DGUV (German statutory accident assurance) VT 266.1.

SAPALDIA received funds from the Swiss National Science Foundation (grants no 33CSCO-134276/1, 33CSCO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099), the Federal Office for Forest, Environment and Landscape and several Federal and Cantonal authorities.

References

- 1 Sunyer J. Lung function effects of chronic exposure to air pollution. *Thorax* 2009; 64: 645–646.
- 2 Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J Med Toxicol* 2012; 8: 166–175.
- 3 Gehring U, Gruzjeva O, Agius RM, et al. Air pollution exposure and lung function in children: The ESCAPE Project. *Environ Health Perspect* 2013; 121: 1357–1364.
- 4 Forbes LJ, Kapetanakis V, Rudnicka AR, et al. Chronic exposure to outdoor air pollution and lung function in adults. *Thorax* 2009; 64: 657–663.
- 5 Ackermann-Lieblich U, Leuenberger P, Schwartz J, et al. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 1997; 155: 122–129.
- 6 Gotschi T, Heinrich J, Sunyer J, et al. Long-term effects of ambient air pollution on lung function: a review. *Epidemiology (Cambridge, Mass)* 2008; 19: 690–701.
- 7 Schikowski T, Sugiri D, Ranft U, et al. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respir Res* 2005; 6: 152.
- 8 Downs SH, Schindler C, Liu LJ, et al. Reduced exposure to PM10 and attenuated age-related decline in lung function. *N Engl J Med* 2007; 357: 2338–2347.
- 9 Eckel SP, Louis TA, Chaves PH, et al. Modification of the association between ambient air pollution and lung function by frailty status among older adults in the Cardiovascular Health Study. *Am J Epidemiol* 2012; 176: 214–223.
- 10 Eeftens M, Beelen R, de Hoogh K, et al. Development of Land Use Regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol* 2012; 46: 11195–11205.
- 11 Beelen R, Hoek G, Vienneau D, et al. Development of NO₂ and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. *Atmos Environ* 2013; 72: 10–23.
- 12 Beelen R, Raaschou-Nielsen O, Stafoggia M, et al. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014; 383: 785–795.
- 13 Eeftens M, Tsai MY, Ampe C, et al. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO₂ - Results of the ESCAPE project. *Atmos Environ* 2012; 62: 303–317.
- 14 Cyrus J, Eeftens M, Heinrich J, et al. Variation of NO₂ and NO_x concentrations between and within 36 European study areas: results from the ESCAPE study. *Atmos Environ* 2012; 62: 374–390.
- 15 Gulliver J, de Hoogh K, Hansell A, et al. Development and back-extrapolation of NO₂ land use regression models for historic exposure assessment in Great Britain. *Environ Sci Technol* 2013; 47: 7804–7811.
- 16 Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007; 30: 616–622.
- 17 Schikowski T, Schaffner E, Meier F, et al. Improved air quality and attenuated lung function decline: modification by obesity in the SAPALDIA cohort. *Environ Health Perspect* 2013; 121: 1034–1039.
- 18 Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006; 130: 827–833.
- 19 Pistelli F, Bottai M, Carrozzi L, et al. Changes in obesity status and lung function decline in a general population sample. *Respir Med* 2008; 102: 674–680.
- 20 Mancuso P. Obesity and lung inflammation. *J Appl Physiol* 2010; 108: 722–728.
- 21 Dubowsky SD, Suh H, Schwartz J, et al. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect* 2006; 114: 992–998.
- 22 Madrigano J, Baccarelli A, Wright RO, et al. Air pollution, obesity, genes and cellular adhesion molecules. *Occup Environ Med* 2010; 67: 312–317.
- 23 Johnston RA, Theman TA, Lu FL, et al. Diet-induced obesity causes innate airway hyperresponsiveness to methacholine and enhances ozone-induced pulmonary inflammation. *J Appl Physiol* 2008; 104: 1727–1735.
- 24 Shore SA, Lang JE, Kasahara DI, et al. Pulmonary responses to subacute ozone exposure in obese vs. lean mice. *J Appl Physiol* 2009; 107: 1445–1452.
- 25 Alexeeff SE, Litonjua AA, Suh H, et al. Ozone exposure and lung function: effect modified by obesity and airways hyperresponsiveness in the VA normative aging study. *Chest* 2007; 132: 1890–1897.

- 26 Bennett WD, Hazucha MJ, Folinsbee LJ, *et al.* Acute pulmonary function response to ozone in young adults as a function of body mass index. *Inhal Toxicol* 2007; 19: 1147–1154.
- 27 Gotschi T, Sunyer J, Chinn S, *et al.* Air pollution and lung function in the European Community Respiratory Health Survey. *Int J Epidemiol* 2008; 37: 1349–1358.
- 28 Gerbase MW, Dupuis-Lozeron E, Schindler C, *et al.* Agreement between spirometers: a challenge in the follow-up of patients and populations?. *Respiration* 2013; 85: 505–514.
- 29 Basagana X, Rivera M, Aguilera I, *et al.* Effect of the number of measurement sites on land use regression models in estimating local air pollution. *Atmos Environ* 2012; 54: 634–642.
- 30 Wang M, Beelen R, Eeftens M, *et al.* Systematic Evaluation of land use regression models for NO₂. *Environ Sci Technol* 2012; 46: 4481–4489.