Association of ambient air pollution with the prevalence and incidence of COPD

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ABSTRACT The role of air pollution in chronic obstructive pulmonary disease (COPD) remains uncertain.

The aim was to assess the impact of chronic exposure to air pollution on COPD in four cohorts using the standardised ESCAPE exposure estimates. Annual average particulate matter (PM), nitrogen oxides (NO_x) and road traffic exposure were assigned to home addresses using land-use regression models. COPD was defined by NHANES reference equation (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) less than the lower limit of normal) and the Global Initiative for Chronic Obstructive Lung Disease criterion (FEV_1/FVC <0.70) and categorised by severity in non-asthmatics.

We included 6550 subjects with assigned NO_x and 3692 with PM measures. COPD was not associated with NO_2 or PM_{10} in any individual cohort. In meta-analyses only NO_2, NO_x, PM_{10} and the traffic indicators were positively, although not significantly, associated with COPD. The only statistically significant associations were seen in females (COPD prevalence using GOLD: OR 1.57, 95% CI 1.11–2.23; and incidence: OR 1.79, 95% CI 1.21–2.68).

None of the principal results were statistically significant, the weak positive associations of exposure with COPD and the significant subgroup findings need to be evaluated in further well standardised cohorts followed up for longer time, and with time-matched exposure assignments.

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Introduction

Ambient air pollution results in adverse acute respiratory effects in populations of all ages [1]. These effects include short-term decreases in lung function, respiratory symptoms, asthma attacks and worsening of chronic obstructive pulmonary diseases (COPD), and related increases in hospitalisations and death due to respiratory causes [2–4]. It is less clear to what extent long-term exposure to air pollution contributes to the pathologic processes and mechanisms that result in COPD [5].

COPD is a common chronic disease of the respiratory tract in the elderly and hence the most common cause of respiratory insufficiency [6]. Due to the slow progression and chronic nature of the disease, COPD represents a massive and growing disease burden and is an important cause of morbidity and mortality worldwide [7]. Tobacco smoke is recognised as the most important risk factor for the development and the progression of COPD. Although tobacco smoke and combustion-related air pollution emit a range of pollutants in common, the role of ambient air pollution on the underlying chronic disease processes that ultimately lead to COPD are not well investigated. An effect of ambient air pollution on lung growth during childhood has been reported [8], but the link between impaired lung development and COPD in future life is not established. Similarly, if repeated exacerbations of COPD are considered a cause of disease progression, one may claim indirect evidence for a causal role of air pollution on COPD, given the ability of air pollution to trigger exacerbations [9].

However, few studies have addressed the COPD hypothesis in adults directly, and only five studies have used spirometry to define COPD objectively [5].

Accordingly, the overall evidence that long-term exposure to ambient air pollution causes COPD among adults was considered suggestive but not conclusive in both an American Thoracic Society statement and a recent update of the literature [10]. A causal role of ambient air pollution in the development of COPD is, though, biologically plausible. Oxidative stress and inflammation have been described as consequences of exposure to several air pollutants [11, 12]. Both pulmonary and systemic effects have been observed and these pathways are likely contributors to respiratory pathologies related to COPD.

The ESCAPE project (European Studies on Chronic Air Pollution Effects) was initiated to provide standardised procedures to measure and model home outdoor concentrations of air pollution to investigate its long-term health effects. This paper makes use of four cohort studies participating in ESCAPE, namely the European Community Respiratory Health Survey (ECRHS), the Medical Research Council National Survey of Health and Development (NSHD), the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) and the Swiss cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), to investigate the association of ambient air pollution with the prevalence and incidence of COPD [13–19].

Methods

Study populations

The analyses are based on random samples of the general population from four cohort studies. All studies performed lung function measurements on two occasions (called baseline and follow-up). To be included in the ESCAPE analyses, participants of the original cohort studies had to be at least 20 years old at baseline; have valid lung function data on two occasions; have available information for the primary covariates; be living in geographic areas where the ESCAPE project derived exposure models; and have at least one successfully assigned home outdoor estimate of exposure (NO_2/NO_x or particulate matter (PM)) (figs S1–S4).

Definition of COPD

In all cohort studies, only pre-bronchodilator spirometric measurements were available. Therefore, to reduce the risk of asthma/COPD misclassification, subjects who reported ''ever asthma'' or a diagnosis of asthma either at baseline or follow-up were excluded from the analyses [20].

COPD was defined according to both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [17] and the lower limit of normal (LLN) (definitions in online supplementary material: methods). As results did not materially differ we only present the LLN results (GOLD results can be found in the online supplementary material). NHANES (National Health and Nutrition Examination Survey) III equations were used as reference [21].

Exposure assessment

The common ESCAPE exposure assessment approaches have been published elsewhere [22, 23]. In summary, standardised measurement protocols were used in all geographic sites of ESCAPE (www.escapeproject.eu/manuals/). In all 24 sites included from the four studies, NO_2/NO_x measurements were conducted in three seasons in 2008–2011 using passive samplers. In 12 ESCAPE locations, PM monitoring

campaigns were conducted. Land use regression models (LUR) described the spatial distributions of the annual mean concentrations taken as a proxy for the long-term averages for all ESCAPE exposure markers. These models were used to assign exposure estimates to each residential address of all study participants. Two markers of local exposure to traffic related pollutants were also derived for each address, namely annual mean traffic intensity on the nearest road, and total traffic load on major roads in a 100-m buffer.

Back extrapolation

Baseline clinical measurements and interviews occurred up to 25 years prior to the ESCAPE measurement campaigns in 2008–2011. In light of the substantial changes, usually decreases, in air pollution during these decades, ESCAPE exposure values were back-extrapolated to correct for the differential time trends of pollution. Back extrapolation was conducted by assuming within-city spatial patterns to remain constant, hence individually assigned estimates of ambient concentrations could be adjusted (calibrated) for the long-term trends using a pre-defined back extrapolation algorithm (www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf).

Thus, wherever available, individual estimates of the home outdoor air pollutant concentrations at the time of the baseline and/or follow-up surveys could be derived.

Statistical analyses

Data from the studies were analysed separately in each cohort following an identical pre-defined analytic code, applied to the study data, and the results then combined by meta-analyses. All studies used identical codebooks to define and name variables.

In the first step, cohort-specific models were defined *a priori*, based on current knowledge. All models were run for the default exposure metrics and for the primary COPD outcomes, namely 1) prevalence of COPD at follow-up and 2) incidence of COPD at follow-up, using GOLD in severity stages 1+ and 2+.

Logistic regression models were used in each study separately to obtain study-specific estimates with a random intercept for area. Several alternative sets of potential confounders were considered in the analyses (online supplementary material: methods). However, only the estimates obtained by our ''main model'', adjusting for age, age squared, height, sex, body mass index, education and smoking status, are reported in the paper, since the diverse models yielded very similar results.

Sensitivity analyses explored whether the use of a different definition for COPD, whether moving residence between baseline and follow-up or whether adding an aggregate socio-economic level of the residential neighbourhood might change observed associations.

In a second step a random-effect meta-analysis of all the cohort-specific estimates obtained by the main model (model 3) was performed to provide overall estimates (the same procedure was used also in specific subgroups and/or for sensitivity analyses).

All models were fitted to the data using Stata, version 12 (StataCorp, College Station, TX, USA).

Results

Study characteristics

In total, 6550 subjects with NO_2 and 3692 subjects with PM10 measurements were available, respectively. The number of participants per cohort varied from 580 (SALIA cohort) to 3194 (ECRHS cohort). Table 1 provides distributions of main covariates of the study populations used in the analyses with NO_2/NO_x (population F1) and those with assigned with all PM measurements (F2) included in these analyses (figs S1–S4).

The distributions of COPD prevalence and incidence and the staging of severity are presented in table 2, stratified also by sex and smoking status. Baseline assessment years were 1985–1999 and follow-up years were 2001–2010. The cohorts included in this study were heterogeneous in composition, with an average age at follow-up ranging from 43 years (ECRHS) to 73 years (SALIA). The SALIA cohort only included females, whereas the other cohorts had an even distribution of males and females (table 1).

The highest prevalence of COPD (all stages) was observed in the SAPALDIA cohort (15.7%; n=276) and the lowest in the NSHD cohort (2.80%; n=23); the same pattern was observed for incidence of COPD (table 2).

Air pollution estimates

Table 3 shows the distribution of the air pollution metrics for each study area. Prediction of LUR models was generally good: the R^2 for PM2.5 models varied between 67% and 88% [23], for NO_2 the R^2 varied between 55% and 90% [22] (table S3). The range of study mean values of PM2.5 varied from 9.5 $\mu g \cdot m^{-3}$ in

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TABLE 1 Description of study populations of all four cohort studies as used in the chronic obstructive pulmonary disease prevalence analyses

	ECRHS		NSHD		SALIA		SAPALDIA	
	NO_2 population	PM population	NO_2 population	PM population	NO_2 population	PM population	NO_2 population	PM population
Subjects n	3194	1583	844	751	580	580	1764	729
Female	1613 (50.5)	830 (52.4)	471 (55.81)	418 (55.6)	580 (100)	580 (100)	980 (55.5)	422 (57. 9)
Age at baseline[#]	34.3±7.2	35.1±7.1	53.4±0.2	53.4±0.2	54.3±0.8	54.3±0.8	42.4±11.0	43.0±10.8
Age at follow-up	43.0±7.2	43.9±7.1	63.3±1.1	63.3±1.1	73.3±3.4	73.3±3.4	53.2±11.0	53.9±10.7
BMI at follow-up kg·m^{-3}	25.4±4.3	24.8±4.3	27.7±4.9	27.7±5.0	27.4±4.5	27.4±4.5	25.4±4.3	25.1±4.3
Smoking status at baseline								
Never-smoker	1390 (43.5)	707 (44.7)	270 (32.0)	230 (30.6)	459 (79.1)	459 (79.1)	704 (39.9)	291 (39)
Ex-smoker	691 (21.6)	494 (31.2)	437 (51.8)	396 (52.7)	61 (10.5)	61 (10.5)	568 (32.2)	219 (30.0)
Current smoker	1113 (34.8)	382 (24.1)	137 (16.2)	125 (16.6)	60 (10.3)	60 (10.3)	492 (27.9)	219 (30.0)
Pack years smoked by ever-smokers at baseline	7.5±11.6	7.4±12.2	9.1±12.6	9.3±12.6	2.8±8.4	2.8±8.4	10.9±17.9	11.8±19.3
Pack years smoked during the follow-up by ever-smokers	3.7±10.5	2.7±10.7	0.7±2.5	0.7±2.5	0.6±6.7	0.6±6.7	3.1±6.5	3.5±6.8
Educational level[¶]								
Low	758 (23.7)	363 (22.9)	303 (35.9)	275 (36.6)	105 (18.1)	105 (18.1)	130 (5.8)	46 (6.3)
Medium	1064 (33.3)	513 (32.4)	439 (52.0)	394 (52.5)	276 (47.6)	276 (47.6)	1121 (63.55)	510 (70.0)
High	1372 (50.0)	707 (44.7)	102 (12.1)	82 (10.9)	199 (34.3)	199 (34.3)	520 (29.5)	172 (23.6)
ETS[+]	555 (17.4)	259 (16.4)	168 (19.9)	144 (19.2)	347 (59.8)	347 (59.8)	119 (6.8)	40 (5.5)
Occupational exposure[§]	1360 (43.4)	549 (35.7)	246 (29.1)	220 (29.3)	39 (6.7)	39 (6.7)	460 (26.1)	143 (19.6)
Asthma at baseline	229 (7.2)	143 (9.1)	44 (5.2)	37 (4.9)	9 (1.6)	9 (1.6)	130 (7.4)	43 (5.9)
Asthma at follow-up	334 (10.5)	191 (12.1)	83 (9.8)	68 (9.1)	47 (8.1)	47 (8.1)	153 (8.7)	48 (6.6)

Subpopulations of the original studies with individually assigned NO_2 and particulate matter (PM) measures, respectively. Data are presented as n (% of total N) for categorical variables, and mean±SD in case of continuous variables. BMI: body mass index; ETS: environmental tobacco smoke. [#]: age at lung function testing; [¶]: maximal reached educational level at baseline and follow-up; [+]: exposure at home or at work at follow-up; [§]: exposure to dust/fumes or gases at follow-up (yes/no).

the NSHD study to 17.8 μg·m^{-3} in the SALIA cohort. Within-study contrasts were smaller for the SALIA and SAPALDIA studies given the smaller geographic study region. The highest average traffic loads were observed in ECRHS and SAPALDIA study sites, the lowest in the NSHD study. Correlations between the individually assigned air pollution estimates are presented in table S2a–d in the online supplement. The highest correlation was observed for NO_2 and NO_x in all cohorts (⩾0.91), whereas correlations between other pollutants and traffic indicators were heterogeneous across sites, ranging from moderate to low.

Back extrapolation to baseline for NO_2 and PM10 was possible in all studies, except in ECRHS, where it was only available for follow-up (2001). The back extrapolated PM10 concentrations between studies varied between 22.0 μg·m^{-3} and 47.7 μg·m^{-3} at baseline, respectively (table 3).

Association between air pollution and COPD prevalence and incidence defined according to the LLN

In the main analyses for prevalence of COPD defined according to the LLN stage 1+, a positive but not statistically significant association was observed for PM10 (OR 1.04, 95% CI 0.71–1.53, per 10 μg·m^{-3}) NO_2 (OR 1.07, 95% CI 0.91–1.26, per 10 μg·m^{-3}) and NO_x (OR 1.07, 95% CI 0.96–1.21, per 20 μg·m^{-3}) (table 4). COPD prevalence was also positively but not significantly associated with traffic intensity on the nearest major road and the traffic load within 100 m of the residency (table 4).

With the exception of PM_{coarse} all exposure variables were positively associated, albeit not significantly, with incidence of COPD using LLN stage 1+ (table 4). Additional adjustment for covariates did not change the main results (data not shown). Associations for both prevalence and incidence of COPD stage 2+ showed similar patterns as for COPD stage 1+ but with wider confidence intervals, related to smaller numbers involved (data not shown).

Association between air pollution and COPD prevalence and incidence defined according to the GOLD

Associations using GOLD definitions showed similar patterns to those using LLN (table S5), except that associations with traffic intensity were statistically significant and that incidence clearly showed positive albeit nonsignificant associations with NO_2/NO_x and PM measures. Associations with COPD incidence were stronger in females than males (figs 1–4 and table S5). Similarly, a higher point estimate could be observed in never-smokers and non-movers (data not shown).

TABLE 2 Prevalence and incidence of chronic obstructive pulmonary disease in all stages (1+) and in stage 2+ using the lower limit of normal at follow-up

	All	Females	Males	Ever-smoker	Never-smoker
ECRHS					
NO_2 population	3194	1613	1581	1804	1390
Prevalence					
All stages	109 (3.41)	54 (3.35)	55 (3.48)	69 (3.82)	40 (2.88)
Stage 2+	39 (1.22)	17 (1.05)	22 (1.39)	29 (1.61)	10 (0.72)
Incidence					
All stages	41 (1.28)	22 (1.36)	19 (1.20)	24 (1.33)	17 (1.22)
Stage 2+	99 (0.28)	5 (0.31)	4 (0.25)	4 (0.22)	5 (0.36)
PM population	1583	830	753	836	747
Prevalence					
All stages	56 (0.95)	29 (3.49)	27 (3.59)	33 (3.95)	23 (3.08)
Stage 2+	15 (0.95)	6 (0.72)	9 (1.20)	11 (1.32)	4 (0.54)
Incidence					
All stages	22 (1.39)	13 (1.57)	9 (1.20)	12 (1.44)	10 (1.34)
Stage 2+	5 (0.32)	3 (0.36)	2 (0.27)	2 (0.24)	3 (0.40)
NSHD					
NO_2 population	844	471	373	574	270
Prevalence					
All stages	29 (3.44)	18 (3.82)	11 (2.95)	26 (4.53)	3 (1.11)
Stage 2+	20 (2.37)	15 (3.18)	5 (1.34)	18 (3.14)	2 (0.74)
Incidence					
All stages	20 (2.37)	12 (2.55)	8 (2.14)	17 (2.96)	3 (1.11)
Stage 2+	14 (2.37)	10 (2.12)	4 (1.07)	12 (2.09)	2 (0.74)
PM population	751	418	333	521	230
Prevalence					
All stages	26 (3.46)	15 (3.59)	11 (3.30)	23 (4.41)	3 (1.30)
Stage 2+	18 (2.40)	13 (3.11)	5 (1.50)	16 (3.07)	2 (0.87)
Incidence					
All stages	19 (2.53)	11 (2.63)	8 (2.40)	16 (3.07)	3 (1.30)
Stage 2+	13 (1.73)	9 (2.15)	4 (1.20)	11 (2.11)	2 (0.87)
SALIA					
NO_2 population	580	580		121	459
Prevalence					
All stages	25 (4.31)	25 (4.31)		9 (7.44)	16 (3.49)
Stage 2+	17 (2.93)	17 (2.93)		7 (5.79)	10 (2.18)
Incidence					
All stages	18 (3.10)	18 (3.10)		7 (5.79)	11 (2.40)
Stage 2+	12 (2.07)	12 (2.07)		5 (4.13)	7 (1.53)
PM population	580	580		121	459
Prevalence					
All stages	25 (4.31)	25 (4.31)		9 (7.44)	16 (3.49)
Stage 2+	17 (2.93)	17 (2.93)		7 (5.79)	10 (2.18)
Incidence					
All stages	18 (3.10)	18 (3.10)		7 (5.79)	11 (2.40)
Stage 2+	12 (2.07)	12 (2.07)		5 (4.13)	7 (1.53)
SAPALDIA					
NO_2 population	1764	980	784	998	766
Prevalence					
All stages	189 (10.71)	64 (6.53)	125 (15.94)	190 (19.04)	86 (11.23)
Stage 2+	61 (3.46)	44 (4.49)	17 (2.17)	61 (6.11))	21 (2.74)
Incidence					
All stages	105 (2.04)	47 (4.80)	58 (7.40)	118 (11.82)	70 (9.14)
Stage 2+	36 (2.04)	30 (3.06)	6 (0.77)	34 (3.41)	14 (1.83)
PM population	729	422	307	406	323
Prevalence					
All stages	58 (7.96)	22 (5.21)	43 (14.01)	62 (15.27)	30 (9.29)
Stage 2+	26 (3.57)	15 (3.55)	12 (3.91)	25 (6.16)	9(2.79)
Incidence					
All stages	41(5.62)	18 (4.27)	34 (11.07)	18 (4.43)	27 (8.36)
Stage 2+	16 (2.19)	11 (2.61)	7 (2.28)	51 (12.56)	6 (1.86)

All four study populations are stratified by sex, and smoking status for population with NO_2 and particulate matter (PM) measures, respectively. Data are presented as N or n (% of total N).

For both the LLN and GOLD definitions of COPD prevalence and incidence, using back-extrapolated exposure metrics instead of exposure metrics derived for the period of air pollution monitoring campaigns did not change the results (data not shown).

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Discussion

The findings of this multicentre European study on air pollution and COPD were inconclusive. Estimated long-term residential exposure to NO_2, PM10 and traffic intensity on the nearest major road was positively but not statistically significantly associated with a higher COPD prevalence in four adult European cohort studies. COPD prevalence was not associated with PM2.5, PM2.5(abs), and PMcoarse with substantial heterogeneities between study and subgroups. The positive association between traffic intensity on the nearest major road and GOLD-defined COPD reached statistical significance only in females (prevalence and incidence) and never smokers (incidence).

Direct comparison with previous studies is in general limited due to differences in study design, exposure assessment, definition of COPD and statistical methods. ESCAPE is the first large-scale multi-cohort study using fully standardised exposure measurement, modelling, and assignment methods, which offers a unique opportunity to evaluate the potential influence of different exposure metrics and model validity on the heterogeneity of results. Most interestingly, as seen in the correlation matrix (table S2), the different metrics of pollution co-vary differently among the geographic regions of these cohorts. For example, whereas NO_2 is rather highly correlated with PM10 in three studies, this is far less the case in the NSHD geography (R=0.43). Similarly, PM2.5(abs) and PMcoarse are poorly correlated in NSHD but rather well correlated in the other

TABLE 3 Distribution of all available exposure metrics (air pollutants and traffic variables) by study

	N	Mean	SD	Min.	25th percentile	50th percentile	75th percentile	Max.	Interquartile range
ECRHS									
PM2.5 $\mu g \cdot m^{-3}$	1582	16.13	6.02	8.17	10.26	16.89	17.96	34.37	7.70
PM2.5(abs) 10^{-5} m^{-1}	1320	2.01	0.91	0.83	1.15	1.82	2.70	5.25	1.55
PM10 $\mu g \cdot m^{-3}$	1583	25.88	9.81	11.91	16.79	24.44	29.38	55.17	12.60
PMcoarse $\mu g \cdot m^{-3}$	1582	10.20	4.69	3.89	6.40	8.80	11.31	25.37	4.91
NO_2 $\mu g \cdot m^{-3}$	1582	28.95	15.43	0.00	18.76	26.54	37.47	115.52	18.71
NO_x $\mu g \cdot m^{-3}$	1582	50.51	30.43	0.00	31.48	43.03	65.93	223.07	34.45
Traffic on nearest road#	1516	5538	11681	0.00	500	800	7080	143156	6580
Traffic load¶	1516	1.44	3.27	0.00	0.00	0.00	1.66	56.50	1.66
Back-extrapolated PM10 to follow-up+ $\mu g \cdot m^{-3}$	1582	27.04	5.52	16.30	22.31	27.20	30.52	47.11	8.22
Back-extrapolated NO_2 to follow-up+ $\mu g \cdot m^{-3}$	1215	41.56	15.33	13.51	29.30	39.28	50.80	120.68	21.51
NSHD									
PM2.5 $\mu g \cdot m^{-3}$	751	9.52	0.99	8.17	8.72	9.48	10.18	13.49	1.45
PM2.5(abs) 10^{-5} m^{-1}	751	1.05	0.24	0.83	0.88	0.98	1.14	3.20	0.26
PM10 $\mu g \cdot m^{-3}$	751	15.73	2.09	11.79	14.67	15.73	16.54	26.20	1.88
PMcoarse $\mu g \cdot m^{-3}$	751	6.37	0.92	5.57	5.78	6.04	6.56	9.71	0.77
NO_2 $\mu g \cdot m^{-3}$	751	22.39	7.13	12.93	16.64	21.83	26.67	61.99	10.03
NO_x $\mu g \cdot m^{-3}$	751	37.54	14.19	19.75	27.22	36.05	44.35	145.43	17.13
Traffic on nearest road#	751	1239	4091	500	500	500	500	76224	0.00
Traffic load¶	751	0.27	0.91	0.00	0.00	0.00	0.00	10.00	0.00
Back-extrapolated PM10 to baseline+ $\mu g \cdot m^{-3}$	748	22.00	2.82	16.37	20.65	21.97	23.28	36.38	2.63
Back-extrapolated NO_2 to baseline+ $\mu g \cdot m^{-3}$	748	26.38	8.40	14.64	20.13	25.74	31.55	70.18	11.42
SALIA									
PM2.5 $\mu g \cdot m^{-3}$	580	17.76	1.33	15.90	16.87	17.26	18.53	21.90	1.70
PM2.5(abs) 10^{-5} m^{-1}	580	1.43	0.41	0.97	1.18	1.30	1.58	3.39	0.40
PM10 $\mu g \cdot m^{-3}$	580	26.72	2.06	23.88	25.40	26.16	27.47	33.47	2.07
PMcoarse $\mu g \cdot m^{-3}$	580	9.37	1.57	2.85	8.50	8.84	10.08	14.79	1.58
NO_2 $\mu g \cdot m^{-3}$	580	27.62	7.52	19.66	22.67	24.24	30.72	70.34	8.05
NO_x $\mu g \cdot m^{-3}$	580	44.16	18.98	23.88	31.86	35.42	52.60	124.34	20.74
Traffic on nearest road#	580	1642	3637	500	500	500	500	27798	0.00
Traffic load¶	580	0.72	2.01	0.00	0.00	0.00	0.32	15.8	0.32
Back-extrapolated PM10 to baseline+ $\mu g \cdot m^{-3}$	580	47.68	8.02	32.24	39.23	49.84	52.79	65.06	13.56
Back-extrapolated NO_2 to baseline+ $\mu g \cdot m^{-3}$	580	35.97	11.52	20.26	27.56	33.32	41.60	84.14	14.04
SAPALDIA									
PM2.5 $\mu g \cdot m^{-3}$	729	16.78	1.62	12.36	16.24	16.78	17.38	23.48	1.13
PM2.5(abs) 10^{-5} m^{-1}	729	1.93	0.38	0.91	1.68	1.96	2.20	3.23	0.52
PM10 $\mu g \cdot m^{-3}$	729	23.16	2.56	17.60	22.32	23.29	24.61	31.69	2.29
PMcoarse $\mu g \cdot m^{-3}$	729	6.49	1.24	4.27	5.53	6.48	7.39	10.39	1.86
NO_2 $\mu g \cdot m^{-3}$	729	26.17	7.65	6.87	22.66	26.64	30.59	56.30	7.93
NO_x $\mu g \cdot m^{-3}$	729	42.02	14.71	4.03	36.55	42.64	49.40	112.16	12.85
Traffic on nearest road#	729	1541	2967	0	0	125	1584	22424	1584
Traffic load¶	729	1.14	1.77	0.00	0.00	0.21	1.75	10.31.	1.75
Back-extrapolated PM10 to baseline+ $\mu g \cdot m^{-3}$	726	46.18	4.45	33.82	44.42	45.51	48.42	61.90	4.00
Back-extrapolated NO_2 to baseline+ $\mu g \cdot m^{-3}$	727	45.84	12.28	11.46	39.65	44.82	51.57	96.40	11.93

PM2.5: particulate matter with a diameter of 2.5 μm or less; PM2.5(abs): absorbance of particulate matter with a diameter of 2.5 μm; PM10: particulate matter with a diameter of 10 μm or less; PMcoarse: coarse fraction of PM2.5 to PM10; NO_x: nitrogen oxides. #: cars per day; ¶: traffic load on nearest major road within 100 m buffer presented in millions; +: only back extrapolation to follow-up in 2001 was possible for ECRHS data; back extrapolation to baseline was possible for NSHD (1999), SALIA (1985–1994) and SAPALDIA (1991).

TABLE 4 Adjusted association between all ESCAPE exposures to air pollution (including traffic indicators) and both the prevalence and incidence of chronic obstructive pulmonary disease (COPD) all stages using the lower limit of normal

Exposure[#]	Prevalence of COPD all stages			Incidence of COPD all stages		
	aOR[¶] (95% CI)	I^2	p-value (het.)	aOR[+] (95% CI)	I^2	p-value (het.)
NO_2	1.07 (0.91–1.26)	24.1	p=0.266	1.05 (0.89–1.23)	0.0	p=0.789
NO_x	1.07 (0.96–1.21)	0.0	p=0.857	1.05 (0.89–1.23)	0.0	p=0.602
PM_{10}	1.04 (0.71–1.53)	0.0	p=0.588	1.10 (0.70–1.73)	0.0	p=0.855
$PM_{2.5}$	0.95 (0.47–1.90)	46.6	p=0.132	1.06 (0.73–1.53)	0.0	p=0.645
$PM_{2.5(abs)}$	1.02 (0.69–1.52)	0.0	p=0.393	1.06 (0.67–1.67)	0.0	p=0.703
PM_{coarse}	0.84 (0.33–2.10)	7.0	p=0.358	0.18 (0.01–5.18)	95.2	p=0.000
Traffic intensity on nearest road	1.19 (0.84–1.68)	0.0	p=0.917	1.24 (0.78–1.96)	0.0	p=0.902
Traffic intensity on major road in a 100 m buffer	1.13 (0.72–1.78)	44.3	p=0.146	1.15 (0.77–1.73)	39.5	p=0.175

Results from the random effect meta-analysis from single pollutant models (adjusted odds ratios and 95% confidence intervals), and I^2 (with p-value) test for heterogeneity of effect estimates between cohorts. NO_x: nitrogen oxides; PM_{10}: particulate matter with a diameter of 10 μm or less; $PM_{2.5}$: particulate matter with a diameter of 2.5 μm or less; $PM_{2.5(abs)}$: absorbance of particulate matter with a diameter of 2.5 μm; PM_{coarse}: coarse fraction of $PM_{2.5}$ to PM_{10}. [#]: associations are presented for the following increments in exposure: 10 $\mu g \cdot m^{-3}$ for NO_2, 20 $\mu g \cdot m^{-3}$ for NO_x, 1×10^{-5} m^{-1} for $PM_{2.5}$ absorbance, 5 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, 10 $\mu g \cdot m^{-3}$ for PM_{10}, 5 $\mu g \cdot m^{-3}$ for PM_{coarse}, 5000 vehicle·day^{-1}·m for traffic intensity on the nearest street; and 4 000 000 vehicle·day^{-1}·m for traffic load on major roads within a 100 m buffer. [¶]: adjusted for sex at baseline, smoking at follow-up, maximum educational level, age at follow-up, height at baseline, body mass index (BMI) at follow-up of all participants; associations with traffic intensity and traffic load were additionally adjusted for background NO_2 concentrations. [+]: adjusted for sex at baseline, smoking at baseline, smoking cessation, maximum educational level, age at baseline, height at baseline, BMI at baseline, change in BMI of all participants; associations with traffic intensity and traffic load were additionally adjusted for background NO_2 concentrations.

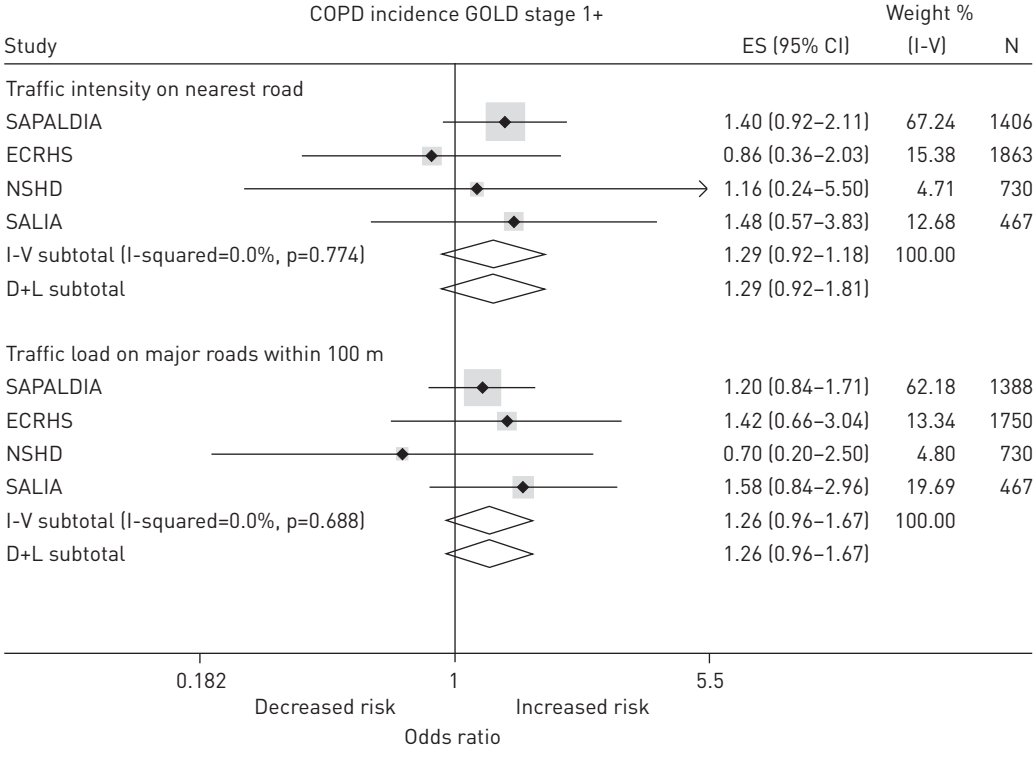

FIGURE 1 Meta-analysis results summarising the centre-specific adjusted random-effect logistic regression model estimates of the effect of traffic variables on incidence of chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria all stages), in all participants, for increments in traffic intensity on the nearest road of 5000 vehicle·day^{-1} and in traffic load on major roads within a 100 m buffer of 500 000 vehicle·day^{-1}·m in two categories. I-squared is the variation in estimate effect attributable to heterogeneity, and D+L the pooled random effects estimate of all studies. The logistic regression models were adjusted for sex at baseline, smoking at follow-up, maximal educational level, age at follow-up, age at follow-up squared, height at baseline, body mass index (BMI) at follow-up and BMI squared. ES: estimate.

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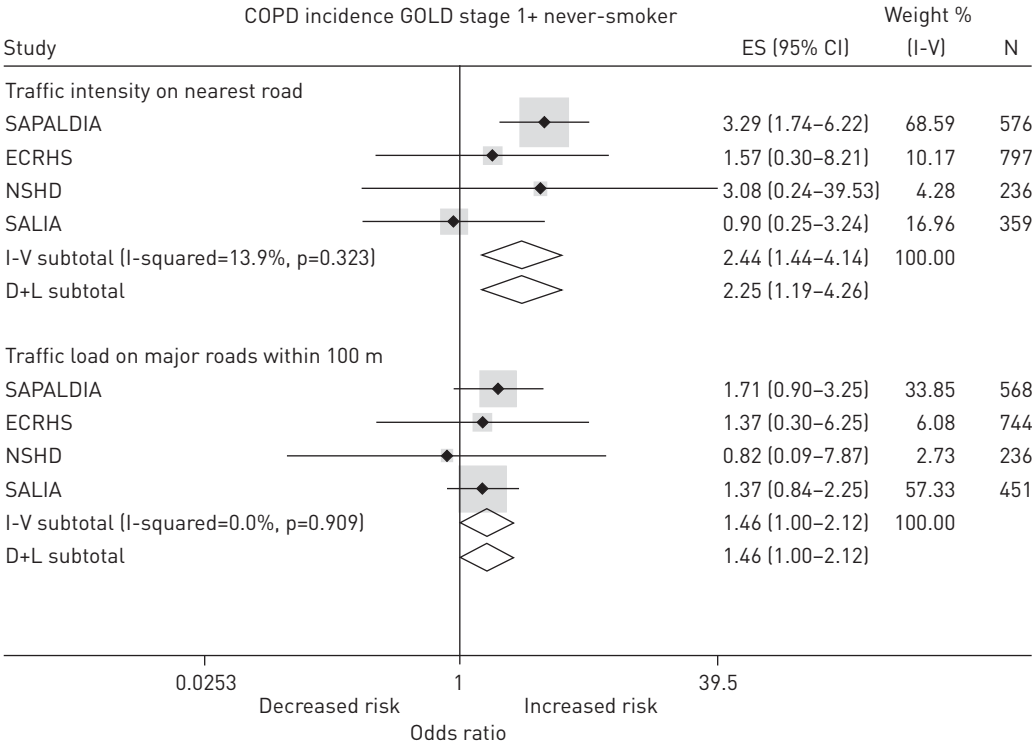

FIGURE 2 Meta-analysis results summarising the centre-specific adjusted random-effect logistic regression model estimates of the effect of traffic variables on incidence of chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria all stages), in never-smokers, for increments in traffic intensity on the nearest road of 5000 vehicle·day^{-1} and in traffic load on major roads within a 100 m buffer of 500 000 vehicle·day^{-1}·m in two categories. I-squared is the variation in estimate effect attributable to heterogeneity, and D+L the pooled random effects estimate of all studies. The logistic regression models were adjusted for sex at baseline, smoking at follow-up, maximal educational level, age at follow-up, age at follow-up squared, height at baseline, body mass index (BMI) at follow-up and BMI squared. ES: estimate.

studies. This highlights the fact that different metrics of pollution may capture different characteristics of the air pollution mixture and that those may vary across regions.

With the exception of PM_{coarse} all associations between air pollutant exposure and COPD prevalence and incidence were positive but not statistically significant. The question arises to what extent uncertainties in the model based assignments of air pollution concentrations may explain the inconclusive findings. A limitation is the time of the ESCAPE exposure measurement. The study used data from measurements performed in 2008–2010 to build the exposure models for each study area. Models were applied to the participants' address of the baseline and the follow-up investigation. However, in some cases the baseline investigation was more than 20 years earlier. To overcome the problem of time discrepancy between exposure measure and examination, we additionally applied a back extrapolation procedure. Findings were, though, weaker when using the back-extrapolated estimates. However, back-extrapolated values have some inherent additional uncertainties. In some centres, routine monitoring stations were not active at the time of baseline investigation. Back extrapolation also relies on the assumption that the spatial pattern was the same in the past as the one observed 2008–2010. A recent publication showed that spatial variation in NO_2 exposure can be reliably estimated retrospectively up to 8 years, also when mean concentrations of air pollutants change over time [24]. Whether this applies also across two decades and to all our sites is less certain. Most importantly, while markers such as NO_2 may well show similar spatial distributions across years and decades, the marker itself may not indicate the same type of pollution mixtures all across these time periods and different geographical areas due to substantial changes in fuel and engine technologies implemented over recent decades.

One should also be aware of inherent limitations in the LUR modelling, adding at least non-systematic uncertainties to the assigned concentrations. The ESCAPE LUR models showed different validity across cities. That could explain some of the between-study heterogeneity. The NO_2 LUR models used in our study sites explained 31 to 88% of the spatial variance with validation R^2 ranging from 55% to 92%. Moreover, it has been shown that the model performance depends on the number of measurement sites used to inform

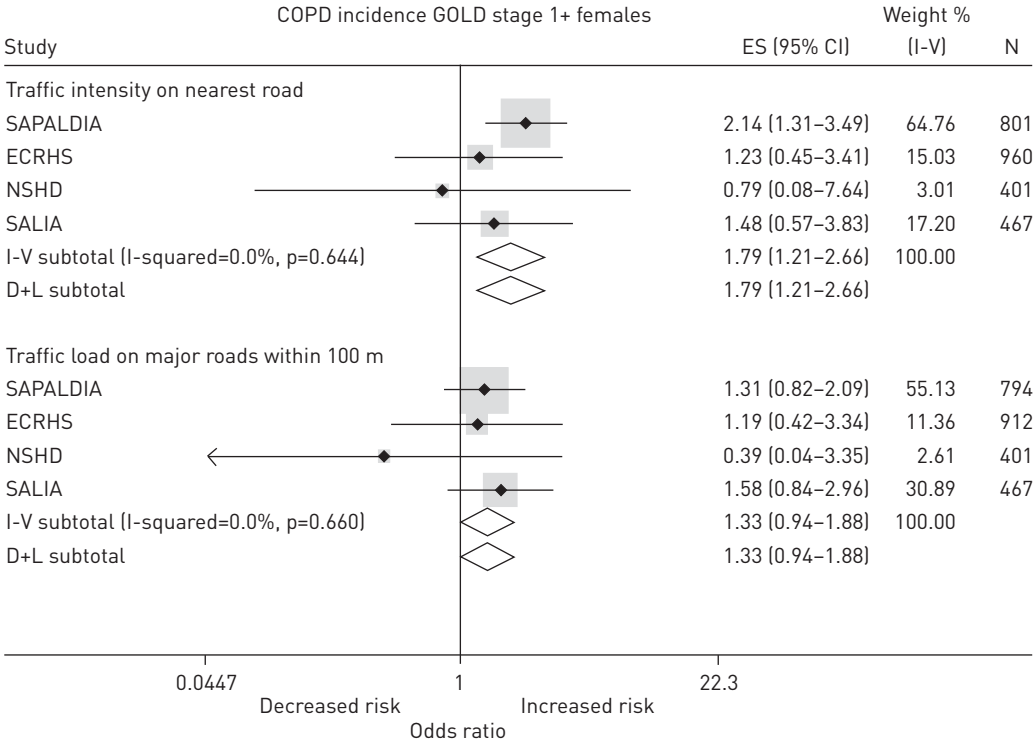

FIGURE 3 Meta-analysis results summarising the centre-specific adjusted random-effect logistic regression model estimates of the effect of traffic variables on incidence of chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria all stages), in females, for increments in traffic intensity on the nearest road of 5000 vehicle·day^{-1} and in traffic load on major roads within a 100 m buffer of 500 000 vehicle·day^{-1}·m in two categories. I-squared is the variation in estimate effect attributable to heterogeneity, and D+L the pooled random effects estimate of all studies. The logistic regression models were adjusted for sex at baseline, smoking at follow-up, maximal educational level, age at follow-up, age at follow-up squared, height at baseline, body mass index (BMI) at follow-up and BMI squared. ES: estimate.

the model, with a tendency to be inflated in models based on the 20–40 default sites of the ESCAPE protocol [25]. Thus, uncertainty in the exposure estimates may be substantial, resulting at least in the need for larger sample sizes to observe more conclusive, statistically significant associations.

SALIA is the only study that previously published on air pollution as well as traffic proximity and COPD prevalence [17]. The published results from the baseline of SALIA around 20 years ago demonstrate that the 5-year mean of PM_{10} showed significant associations not only with forced vital capacity and forced expiratory volume in 1 s but also with the odds of having GOLD defined COPD (stage 1–4): OR 1.68, 95% CI 1.01–2.78, per 10 μg·m^{-3} PM_{10}. However, our ESCAPE analysis showed a nonsignificant association of COPD with PM_{10} in SALIA. A stepwise analysis revealed that restricting to surviving females and using the most recent lung function measurements were most influential in reducing the odds ratio towards null findings. In contrast to the baseline times when particle pollution was much higher, no association between particle pollution and prevalence of COPD was detected in SALIA in 2008. Thus, the previously published results could not be replicated in the smaller subpopulation of SALIA contributing to ESCAPE.

Our findings on the association between prevalence of COPD and traffic-related air pollution in females are partly consistent with those from other studies [26–30]. Kan *et al.* [31] reported that lung function was inversely related to traffic exposure in females. However, it is unclear whether females are more susceptible to the effects of air pollution compared to males. One may also argue that outdoor air quality at home may better reflect exposure in females, as they spend more time near home, on average [32]. Only a few studies have reported sex-specific analyses of air pollution-induced respiratory health effects and the pattern is not conclusive [18, 31, 33]. It is unclear whether the observed modifications of sex are a result of sex-linked biological differences or sex differences in activity pattern [32]. Moreover, we cannot fully separate the possible modification by sex from possible impact of study design differences given that results in females are dominated by SALIA where all were older females.

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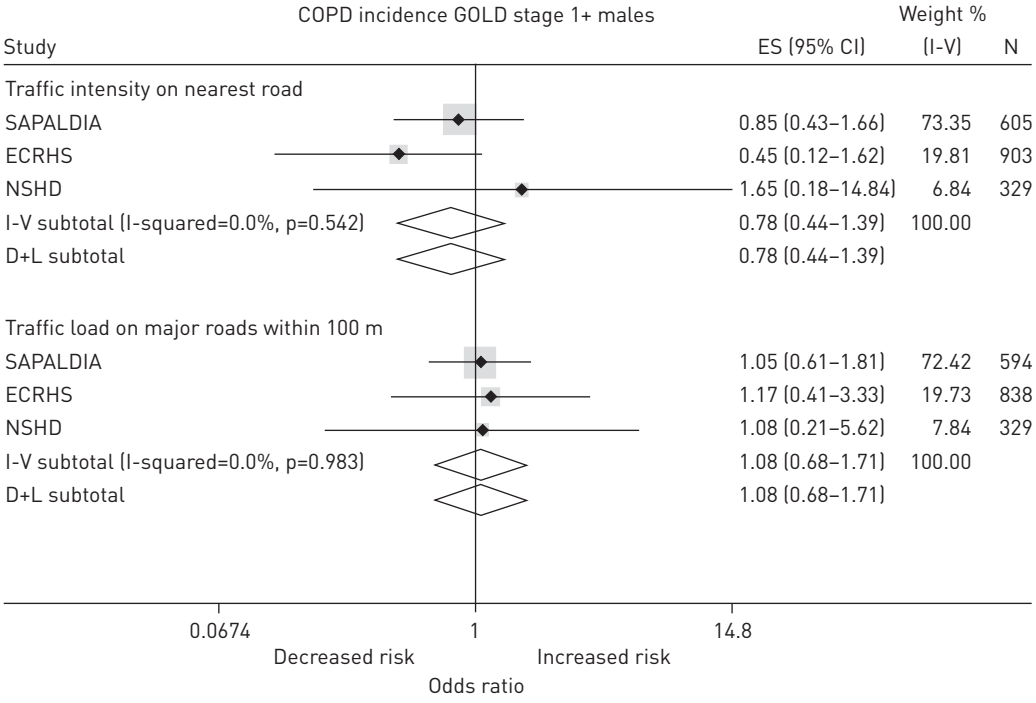

FIGURE 4 Meta-analysis results summarising the centre-specific adjusted random-effect logistic regression model estimates of the effect of traffic variables on incidence of chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria all stages), in males, for increments in traffic intensity on the nearest road of 5000 vehicle·day^{-1} and in traffic load on major roads within a 100 m buffer of 500 000 vehicle·day^{-1}·m in two categories. I-squared is the variation in estimate effect attributable to heterogeneity, and D+L the pooled random effects estimate of all studies. The logistic regression models were adjusted for sex at baseline, smoking at follow-up, maximal educational level, age at follow-up, age at follow-up squared, height at baseline, body mass index (BMI) at follow-up and BMI squared. ES: estimate.

The findings of more consistent and partly significant results for traffic intensity near the residence are interesting. One may argue that exhaust pollutants such as primary ultrafine particles (such as diesel soot) might be captured particularly with those near-road markers of traffic-related pollution. This is in accordance with postulated biological mechanisms that chronic inhalation of such pollutants may damage the lung tissue and hence lead to the development of COPD [27, 34]. However, the heterogeneous findings for $PM_{2.5}$ and in particular for PM reflectance, which is considered to be a good marker for near-road traffic-related pollutants, remain unexplained and inconsistent with our hypotheses, experimental studies and a few epidemiological studies.

Our study has major strength, including the objective definition of COPD, the relatively large number of observations, and the multicentre design across different European regions, which cover different types of environment and climates. We additionally harmonised the exposure assessment methods, and developed a common study protocol for exposure and outcome definition as well as the analytic approach. The limitations discussed above may, however, be rather influential and explain the inconsistencies and uncertainties. Moreover, the use of existing studies instead of prospectively designed very large cohorts comes with the inevitable disadvantage of not fully standardised health outcome and covariate assessment, which adds at least statistical noise to the data. Whether and to what extent this may be a source of systematic differences between studies is not known.

Conclusion

The mostly nonsignificant though positive associations cannot conclusively answer the question of whether traffic-related ambient air pollution may contribute to the development of COPD. Large-scale standardised cohort studies with longer follow-ups are needed to clarify the role of different sources of air pollution on COPD inception and to explain the inconsistent findings of this meta-analysis, especially for PM fractions.

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