

ORIGINAL ARTICLE

Cross-sectional associations between air pollution and chronic bronchitis: an ESCAPE meta-analysis across five cohorts

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2013-204352>).

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TS, FK UK, JS, NK, NP-H and ALH: Steering Committee ESCAPE Work Package 4 Respiratory Health in Adults.

†Deceased.

Received 14 August 2013

Revised 11 July 2014

Accepted 17 July 2014

Published Online First

11 August 2014



CrossMark

To cite: Cai Y, Schikowski T, Adam M, et al. *Thorax* 2014;**69**:1005–1014.

ABSTRACT

Background This study aimed to assess associations of outdoor air pollution on prevalence of chronic bronchitis symptoms in adults in five cohort studies (Asthma-E3N, ECRHS, NSHD, SALIA, SAPALDIA) participating in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project.

Methods Annual average particulate matter (PM₁₀, PM_{2.5}, PM_{absorbance}, PM_{coarse}), NO₂, nitrogen oxides (NO_x) and road traffic measures modelled from ESCAPE measurement campaigns 2008–2011 were assigned to home address at most recent assessments (1998–2011). Symptoms examined were chronic bronchitis (cough and phlegm for ≥3 months of the year for ≥2 years), chronic cough (with/without phlegm) and chronic phlegm (with/without cough). Cohort-specific cross-sectional multivariable logistic regression analyses were conducted using common confounder sets (age, sex, smoking, interview season, education), followed by meta-analysis.

Results 15 279 and 10 537 participants respectively were included in the main NO₂ and PM analyses at assessments in 1998–2011. Overall, there were no statistically significant associations with any air pollutant or traffic exposure. Sensitivity analyses including in asthmatics only, females only or using back-extrapolated NO₂ and PM₁₀ for assessments in 1985–2002 (ECRHS, NSHD, SALIA, SAPALDIA) did not alter conclusions. In never-smokers, all associations were positive, but reached statistical significance only for chronic phlegm with PM_{coarse} OR 1.31 (1.05 to 1.64) per 5 µg/m³ increase and PM₁₀ with similar effect size. Sensitivity analyses of older cohorts showed increased risk of chronic cough with PM_{2.5abs} (black carbon) exposures.

Conclusions Results do not show consistent associations between chronic bronchitis symptoms and current traffic-related air pollution in adult European populations.

Key messages

What is the key question?

► Is long-term exposure to traffic or ambient air pollution associated with prevalence of cough and phlegm in adult European populations?

What is the bottom line?

► Current long-term average air pollution levels were not associated with symptoms of chronic bronchitis, cough or phlegm in European adults of all ages living in nine European countries, but there were small increases in reported phlegm in never-smokers associated with coarse particulate matter.

Why read on?

► This is one of the largest such studies in adults involving >10 000 individuals in five European cohorts using harmonised exposure and outcome measurements; while most results were null, there was some heterogeneity across findings for cohort assessments at different time points, particularly for black carbon and NO₂.

INTRODUCTION

Chronic cough and phlegm production are common respiratory symptoms. In the past, these were often considered together as the clinical phenotype of chronic bronchitis,¹ but more recently phlegm² and cough³ have been considered separately and may have differing mechanisms—for example, cough may result from central reflex sensitivity⁴ as well as irritation and inflammation. A previous study of young adults found wide geographic variability in

chronic bronchitis prevalence (0.7–9.7%) across Europe, but only 30% of the variability could be explained by differences in smoking habits.⁵ This suggests other potentially modifiable factors—such as air pollution—may be important.

There is good evidence that air pollution triggers exacerbations in patients with COPD, and suggestive evidence of chronic effects of air pollution on the prevalence and incidence of COPD in adults.⁶ Concurrent asthma may give rise to cough and phlegm. Traffic-related air pollution has also been related to onset of childhood asthma, but findings in adults are less clear.⁷ Pathophysiological studies have found associations between long-term exposure to ambient particulate matter (PM) and chronic mucosal inflammation in the lung,⁸ resulting in excessive mucus secretion, coughing and phlegm production.⁹ Previous epidemiological studies examining associations between objectively measured air pollution and chronic bronchitis symptoms in adults^{10–27} are difficult to compare. For example, some studies have used surrogate measures for air pollution (eg, distance from the main road,^{13 20 21 27} traffic intensity¹⁷), others used air pollution data from local monitoring networks^{10–13 16 22 23 25 26} or model-derived exposures estimated at home address.^{15 17 19 24} Some^{13 15 17} but not all^{14 18 19 23} studies reported increased risks in the general population, whereas studies in specific populations reported associations only in never-smokers^{10–12 16 26} or females.^{20 21 25}

The present study investigates cross-sectional associations between ambient air pollution estimated at home address and prevalence of chronic bronchitis symptoms in five European cohort studies participating in European Study of Cohorts for Air Pollution Effects (ESCAPE) project. Taking advantage of individual information and repeated assessments, we gave special attention to the time period of exposure (contemporary, historic 2000s and historic 1990s exposures) in repeated cross-sectional analyses and conducted extensive sensitivity analyses.

METHODS

Study populations

Analyses were based on subpopulations from the European Community Respiratory Health Survey (ECRHS); National Survey of Health and Development (NSHD) from the UK; the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) from Ruhr area in Germany; the Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults (SAPALDIA); and the French Asthma-E3N study, an asthma case–control study nested in the ‘Etude Épidémiologique de Femmes de la Mutuelle Générale de l’Education Nationale (E3N)’ cohort who were living in geographic areas covered by ESCAPE exposure models (‘ESCAPE areas’). A brief description of each cohort is available in online supplements-1. Those included in the analyses had valid chronic bronchitis data and information on sex, age, smoking status, season of questionnaire interview, education. The NSHD, SALIA and SAPALDIA contributed information from two assessment rounds. Ethical approvals for analyses were obtained for all cohorts.

Outcome definition

Chronic bronchitis symptoms were assessed by questionnaire in all cohorts using standard questions based on those defined by the British Medical Research Council (MRC) in 1965,¹ as reported cough and phlegm production first thing in the morning and/or during the day or at night for 3 months of the year for ≥ 2 years. Other outcomes investigated were chronic cough (reported cough for 3 months for ≥ 2 years regardless of reported phlegm or not) and chronic phlegm (reported phlegm

for 3 months for ≥ 2 years regardless of reported cough or not), except for SALIA, where questions regarding phlegm production were not asked separately from cough, therefore it was not possible to derive the outcome of ‘chronic phlegm’ (online supplements-2).

Exposure measurements

ESCAPE-period exposures

The ESCAPE exposure assessments have been described elsewhere.^{28 29} Briefly, a standardised protocol was applied in all geographic sites within the ESCAPE areas during October 2008 to April 2011. Nitrogen dioxide (NO₂) and nitrogen oxides (NO_x) measurements were conducted in 36 ESCAPE study areas while PM (PM₁₀, PM with aerodynamic diameter $\leq 10 \mu\text{m}$ and PM_{2.5}, PM with aerodynamic diameter $\leq 2.5 \mu\text{m}$) were measured in 20 ESCAPE study areas, both in a 14-day period of each of three seasons (cold, warm and intermediate). Annual average concentrations for each monitoring site were calculated by combining the three 14-day periods with measurement data from a centrally located reference site, in operation during the whole study period, to adjust for temporal variability. The land-use regression (LUR) model developed used geographic information system (GIS)-derived predictor variables to describe spatial variation of annual average concentrations for each study area at measurement locations. An annual average estimate was then assigned from the LUR models to each geocoded address (place of residence) based on the date of questionnaire assessment for study participants. In addition, two indicators of local exposures to traffic were derived for each participant’s address: traffic intensity on the nearest road (*traffic intensity*, vehicles/day) and total traffic load on major roads in a 100 m buffer (*traffic load*, vehicles*m/day).

Each participant was assigned an annual average concentration at home outdoor of NO₂, NO_x and the background levels of NO₂. For participants residing within ESCAPE areas with PM measurements, they were also assigned exposures to PM_{2.5}, PM₁₀, the coarse fraction of PM (PM_{coarse} as PM₁₀ minus PM_{2.5}) and PM_{2.5abs}, the light absorbance of PM_{2.5} (similar to ‘black carbon’).

Back-extrapolation

Questionnaire assessments in some cohorts occurred prior to the ESCAPE monitoring campaign in 2008–2011, with some up to 25 years earlier. Due to changes (usually decreases) in air pollution over time, ESCAPE-period exposure values were back-extrapolated to the years of collection of health data assuming proportional changes in within-city spatial patterns. Here, individually assigned estimates of ambient concentrations were adjusted (calibrated) for the long-term trends using a predefined back-extrapolation algorithm (see http://www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf; accessed 10 May 2014).

Back-extrapolation for NO₂ and PM₁₀ was conducted by ratio methods to the most recent follow-up years in ECRHS and SAPALDIA (assessments in 1998–2002 and 2002, respectively) and also to earlier assessment in SALIA in 1985–1994, NSHD in 1999 and SAPALDIA in 1991.

Statistical analyses

Each cohort was first analysed separately using centrally written analytic codes, and harmonised outcome and confounder variables. Descriptive analyses were conducted including Spearman correlation coefficients. The analytic strategy, including all models, sensitivity and subgroup analyses, was specified a priori,

based on current knowledge. Cross-sectional analyses using logistic regression models were undertaken to obtain cohort-specific ORs. Results were then combined using both fixed effects and random effects meta-analyses; pooled estimates from the latter were only shown when heterogeneity ($p < 0.05$) existed across cohorts.

The main analyses used 'ESCAPE-period exposure' for 2008–2011 applied to the most recent assessment within 10 years of exposure models in all five cohorts (earliest ECRHS and SAPALDIA with assessments in 2002).

A sequence of nested models were run for each outcome: model 1—unadjusted crude model; model 2—adjustments of age and sex; model 3 (main model)—further adjusted for smoking, education level and interview season, all uniformly defined in all cohorts. Model 4 was further adjusted for environmental tobacco smoking (ETS) exposures at home and/or at work and occupational exposures to any of vapours/gases/dusts/fumes (VGDF); availability and definition of these differed across cohorts. Model 5 was a study-specific model further adjusted for smoking pack years and locally defined neighbourhood-level socioeconomic status. All traffic indicator models were adjusted for the background NO_2 (NO_2 not directly influenced by traffic) to better estimate near traffic effects.

In main analyses, based on model 3 using ESCAPE-period exposures, cohort-specific sensitivity analyses were conducted (i) on the following potentially sensitive subgroups: females, asthmatics, those aged ≥ 50 years and never-smokers; (ii) excluding those with COPD and/or asthma.

All cohort-specific results from model 3 (or where appropriate, related subgroup and/or sensitivity analyses), were then combined using both fixed effects and random effect meta-analyses by the Stata `metan` command; pooled estimates from the latter were only shown when heterogeneity ($p < 0.05$) existed across cohorts. Results presented/used in the meta-analyses for multicountry study ECRHS were from random effect models with city modelled as a random effect while the other four were from fixed effect models with country/area modelled as a fixed effect.

Further sensitivity analyses were conducted to address issues relating to cohort heterogeneity and exposure estimation. In main analyses, based on model 3 using ESCAPE-period exposures, cohort heterogeneity was investigated in leave-one-out meta-analyses, where each cohort was dropped in turn. To investigate exposure issues, we (i) conducted meta-analyses excluding centres with poorer exposure model validation statistics ($R^2 < 0.6$); (ii) restricted analyses to non-movers (those who did not move between the most recent and previous assessment, which were at least 8 years apart); (iii) conducted analyses using 'contemporary exposure estimates'; these used ESCAPE 2008–2011 estimates for Asthma-E3N (2011), NSHD (2008) and SALIA (2006/2010), that is, excluding SAPALDIA and ECHRHS where questionnaire assessments were > 6 years prior to exposure estimation; (iv) conducted analyses using 'historic exposure estimates' back-extrapolated to year of assessment for assessments in 1999–2002 (ECRHS 2002, NSHD 1999, SAPALDIA 2002) and in the early 1990s (SAPALDIA 1991, SALIA 1985–1994), that is, when exposures were higher.

Statistical analyses were performed using Stata V.12.0, Texas, USA. Statistical significance was set at p value < 0.05 .

RESULTS

For main analyses using ESCAPE-period estimates for the most recent assessment, there were 15 279 participants successfully assigned at least NO_2 estimates (table 1) and 10 537 participants

assigned at least PM_{10} estimates (see online supplements-3) with information on variables of main model 3. At the most recent assessment, mean age of the study population ranged from 42.9 years (ECRHS) to 71.5 years (SALIA). Asthma-E3N and SALIA were cohorts of older females only. Current smokers ranged from 5.3% (SALIA) to 32% in the younger general population of ECRHS. Asthma-E3N participants were mainly teachers, and 91.3% were highly educated compared with 11.5% in NSHD. VGDF exposure was 30–40% in the mixed sex general population cohorts (ECRHS, NSHD, SAPALDIA) but lower in the female cohorts. Prevalence of chronic bronchitis ranged from 1.5% (Asthma-E3N) to 6.8% (SALIA) (see online supplements-4).

Summary statistics of ESCAPE-period air pollutants and traffic indicators are presented in online supplements-5. Mean NO_2 ranged from $22 \mu\text{g}/\text{m}^3$ (NSHD) to $31 \mu\text{g}/\text{m}^3$ (Asthma-E3N), whereas mean PM_{10} ranged from $16 \mu\text{g}/\text{m}^3$ (NSHD) to $27 \mu\text{g}/\text{m}^3$ (SALIA). Within-study contrasts assessed by IQR varied from $8 \mu\text{g}/\text{m}^3$ in SAPALDIA to $20 \mu\text{g}/\text{m}^3$ in ECRHS for NO_2 and $2 \mu\text{g}/\text{m}^3$ (NSHD) to $9.2 \mu\text{g}/\text{m}^3$ (ECRHS) for PM_{10} . Exposures back-extrapolated to the 1990s were higher than for estimates at later assessments.

Spearman correlation coefficients between PM and NO_x/NO_2 metrics were high ($r \sim 0.7$ – 0.8), therefore precluding two pollutant analyses, while correlations between pollutants and traffic measures were low to moderate ($r \sim 0.3$ – 0.5) (see online supplements-6).

ESCAPE-period exposure estimates 2008–2011 were highly correlated ($r > 0.9$) with exposures back-extrapolated to the assessments in 2002 ECRHS and SAPALDIA, justifying the use of ESCAPE-period exposures in main analyses.

Results from analyses using ESCAPE-period exposure estimates

Combined estimates from the meta-analyses using model 3 are displayed in table 2 (see also figure 1 and Forest plots, online supplements-7). No statistically significant overall associations were found between any air pollutant or traffic indicator and any outcome using ESCAPE-period estimates.

Associations in meta-analyses using main model 3 leaving out one cohort in turn (online supplements-8) or restricted to cohorts with 'contemporary exposure estimates': Asthma-E3N (2011), NSHD (2008) and SALIA (2006–2010) (online supplements-9) were all null except for associations between chronic cough and $\text{PM}_{2.5\text{abs}}$ in analyses not including ECRHS, with OR, 95% CI 1.20 (1.01 to 1.44) per $10^{-5}/\text{m}$.

Further adjustments in models 4 and 5 did not change the results substantially, although effect estimates were slightly smaller and the 95% CIs became wider (data not shown), which may in part relate to fewer participants.

Sensitive subgroups

In never-smokers, higher and uniformly positive effect estimates for all air pollutants and traffic indicators for all three outcomes were observed (table 3). A statistically significant association was found between chronic phlegm and both PM_{10} (OR, 95% CI 1.32 (1.02 to 1.71), per $10 \mu\text{g}/\text{m}^3$ increase) and $\text{PM}_{\text{coarse}}$ (OR, 95% CI 1.31 (1.05 to 1.64), per $5 \mu\text{g}/\text{m}^3$ increase) (figure 2). In analyses of never-smokers in cohorts with 'contemporary exposure estimates' (online supplements-9), associations with chronic phlegm were no longer statistically significant but associations between chronic cough and $\text{PM}_{2.5}$ and $\text{PM}_{2.5\text{abs}}$ became larger and statistically significant: $\text{PM}_{2.5}$ OR, 95% CI 1.47 (1.02 to 2.12) per $5 \mu\text{g}/\text{m}^3$ increase, $\text{PM}_{2.5\text{abs}}$ OR, 95% CI 1.30 (1.04 to

Table 1 Description of study population (subpopulations of the original study with individually assigned NO₂ measures) of all five cohorts as used at each assessment

Study Co-variables	Asthma-E3N		ECRHS		NSHD				SALIA				SAPALDIA			
	Assessment 2011 N=4070		Assessment 1998–2002 N=5053		Assessment 1999 N=2322		Assessment 2008 N=2024		Assessment 1985–1994 N=4360		Assessment 2006–2010 N=2019		Assessment 1991 N=3766		Assessment 2002 N=2113	
	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD	N/ Mean	% /SD
Female	4070	100%	2712	53.7%	1216	52.4%	1075	53.1%	4360	100%	2019	100%	1949	51.8%	1126	53.3%
Age, years	70.0	6.4	42.9	7.1	53.5	0.2	61.9	0.6	54.5	0.6	71.5	3.4	41.3	11.8	53.1	11.5
Body mass index (BMI), kg/m ²	24.0	4.5	25.7	4.6	27.4	4.7	27.9	4.9	27.6	4.7	26.9	4.3	23.7	3.9	25.5	4.3
Smoking pack years*	3.5	10.2	12.2	18.2	10.3	13.6	10.7	15.2	4.1	10.3	4.3	11.9	11.8	19.0	13.8	22.4
Never-smoker	2770	68.0%	2086	41.3%	708	30.5%	644	31.8%	3230	74.1%	1607	79.6%	1571	41.7%	853	40.4%
Ex-smoker	1041	25.6%	1364	27.0%	1133	48.8%	1141	56.4%	378	8.7%	304	15.1%	809	21.5%	678	32.1%
Current smoker	259	6.4%	1603	31.7%	481	20.7%	239	11.8%	752	17.2%	108	5.3%	1386	36.8%	582	27.5%
Low education	107	2.6%	1471	29.1%	965	41.6%	798	39.4%	1260	28.9%	438	21.7%	574	15.2%	137	6.5%
Medium education	246	6.1%	1732	34.3%	1105	47.6%	994	49.1%	2100	48.2%	986	48.8%	2410	64.0%	1352	64.0%
High education	3717	91.3%	1850	36.6%	252	10.9%	232	11.5%	1000	22.9%	595	29.5%	782	20.8%	624	29.5%
ETS exposures	168	5.1%	506	10.0%	523	25.0%	452	24.6%	2205	50.9%	976	49.2%	518	13.8%	146	6.9%
VGDF exposures	879	23.2%	2146	44.4%	721	35.1%	632	34.8%	428	9.8%	184	9.1%	1060	28.2%	581	27.5%
Asthmatics†	967	26.6%	782	15.5%	221	10.0%	192	9.8%	102	2.4%	121	6.4%	296	7.9%	181	8.6%
COPD Gold stage 1 plus‡	n/a	n/a	305	7.2%	110	6.6%	92	8.2%	289	12.5%	102	15.4%	395	11.4%	399	20.6%

Table shows the N (and % of N) for categorical variables and mean (SD) for continuous variables.

*Calculations based on ex-smokers and current smokers.

†Asthmatics cases were defined as those who answered 'yes' to ever-asthma questions in the questionnaires of all cohorts.

‡Stages of COPD were classified according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) definitions and NHANES III (Third National Health and Nutrition Examination Survey) reference equations. There were no lung function test conducted in Asthma-E3N cohort hence results were n/a (not applicable). Only pre-bronchodilator spirometric measurements were available for all cohorts.

ECRHS, European Community Respiratory Health Survey; ETS, Environmental Tobacco Smoke at home and/or at work; NSHD, National Survey of Health and Development; SALIA, Study on the influence of Air pollution on Lung function, Inflammation and Aging; SAPALDIA, Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults; VGDF, occupational vapour/gases/dust/fumes exposure (any of).

Table 2 Overall populations at the most recent assessment *: fixed-effect meta-analysis results on model 3 (adjusted for age, sex, smoking, education and season of interview) for all air pollutants and traffic indicators for each outcome, using ESCAPE-period (2008–2011) exposures from all five cohorts.

Outcome Exposure†	Chronic bronchitis		Chronic cough		Chronic phlegm	
	OR (95% CI)	P _{het} ‡	OR (95% CI)	P _{het}	OR (95% CI)	P _{het}
PM _{2.5} (5 µg/m ³)	0.90 (0.74 to 1.09)	0.754	0.91 (0.80 to 1.04)	0.440	0.96 (0.84 to 1.11)	0.850
PM _{2.5abs} (per 10 ⁻⁵ m ⁻¹)	1.02 (0.85 to 1.22)	0.504	1.01 (0.89 to 1.15)	0.070	1.02 (0.88 to 1.18)	0.693
PM ₁₀ (10 µg/m ³)	0.92 (0.75 to 1.13)	0.193	0.92 (0.80 to 1.06)	0.494	1.02 (0.87 to 1.18)	0.696
PM _{coarse} (5 µg/m ³)	0.99 (0.83 to 1.18)	0.165	0.99 (0.87 to 1.12)	0.737	1.07 (0.94 to 1.22)	0.131
NO ₂ (10 µg/m ³)	1.00 (0.92 to 1.08)	0.973	1.05 (0.99 to 1.11)	0.953	1.01 (0.95 to 1.07)	0.656
NO _x (20 µg/m ³)	1.02 (0.94 to 1.09)	0.793	1.04 (0.98 to 1.09)	0.622	1.02 (0.96 to 1.08)	0.393
Traffic intensity§	0.95 (0.75 to 1.19)	0.739	0.96 (0.80 to 1.14)	0.339	0.98 (0.82 to 1.17)	0.366
Traffic load¶	0.99 (0.82 to 1.20)	0.509	0.95 (0.81 to 1.10)	0.831	0.97 (0.83 to 1.13)	0.797

*Asthma-E3N 2011, ECRHS 1998–2002, NSHD 2008, SALIA 2006–10, SAPALDIA 2002. Due to questionnaire wording SALIA is not included in analyses of phlegm alone.

†Results were interpreted as per exposure unit, as shown in the parentheses.

‡P_{het}: p value for heterogeneity.

§Binary variable, <5000 (reference group) vs >5000 vehs/day.

¶Binary variable, <500 000 (reference group) vs >500 000 vehs m/day.

ECRHS, European Community Respiratory Health Survey; ESCAPE, European Study of Cohorts for Air Pollution Effects; NO_x, nitrogen oxides; NSHD, National Survey of Health and Development; PM, particulate matter; SALIA, Study on the influence of Air pollution on Lung function, Inflammation and Aging; SAPALDIA, Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults.

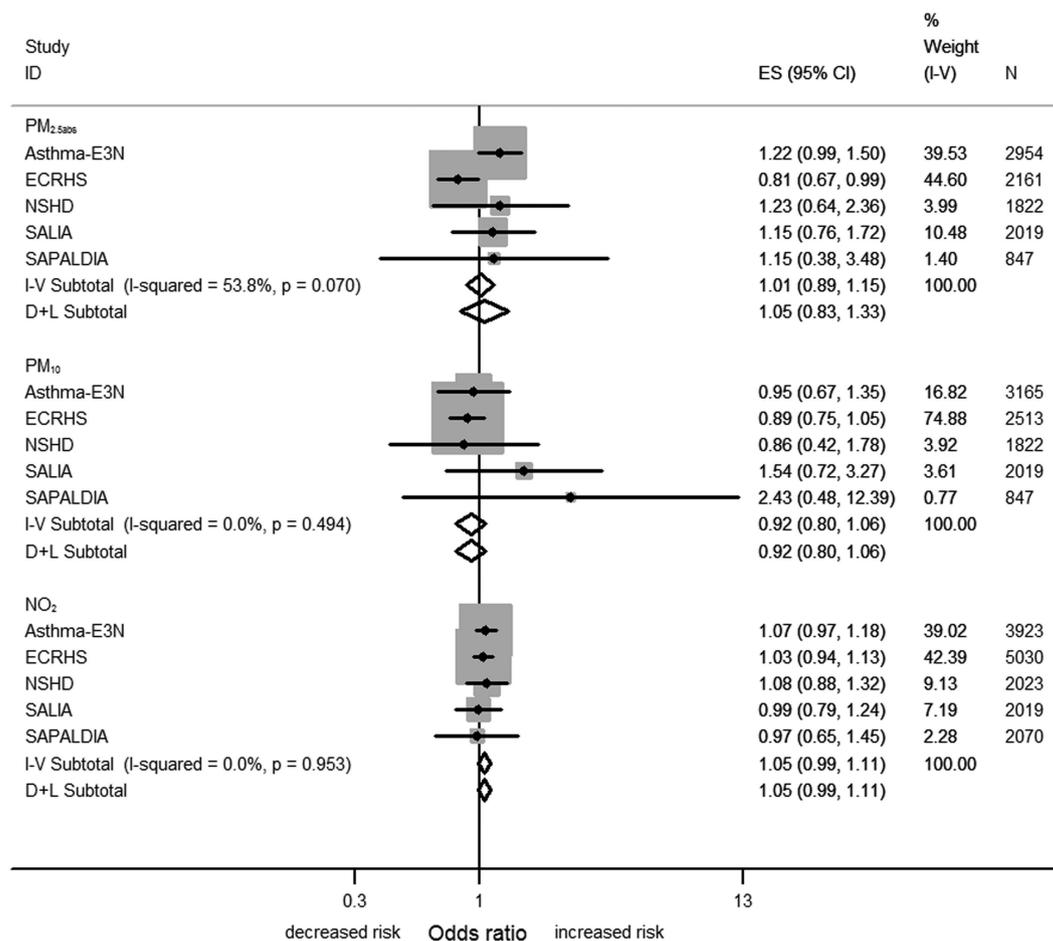


Figure 1 Meta-analysis results on model 3 (adjusted for age, sex, smoking, education, season of questionnaire interview) for NO₂ (per 10 µg/m³), PM₁₀ (per 10 µg/m³) and PM_{2.5abs} (per 10⁻⁵ m⁻¹) for chronic cough at the most recent assessment using the European Study of Cohorts for Air Pollution Effects (ESCAPE)-period exposures in the overall populations from all five cohorts. I-squared, variation in estimated effect attributable to heterogeneity; I-V, inverse-variance weighted fixed effects method; D-L, DerSimonian-Laird random effects method; ES, effect estimate; PM, particulate matter.

1.63) per 10⁻⁵/m, although with evidence of heterogeneity for the latter ($P_{\text{het}}=0.024$). In the random-effects analysis, the PM_{2.5abs} result was not statistically significant: OR, 95% CI 1.58 (0.90 to 2.76) per 10⁻⁵/m.

There were no statistically significant effect estimates observed in meta-analyses for asthmatics, females, participants aged 50+ years, participants without COPD and/or asthma or non-movers (results not shown).

Exposure-related sensitivity analyses

Sensitivity analyses for NO₂ and NO_x excluding centres with LUR model validation R² statistics <0.6 gave similar null results for the main ESCAPE-period analyses (online supplements-10). The R² statistics were all >0.6 for PM estimates in our study areas.

Using back-extrapolated 'historic exposure estimates' to 1999–2002 (table 4), there were consistent but statistically non-significant elevated risks in all populations but not in never-smokers for all three outcomes with NO₂ and PM₁₀. Using historic exposure estimates to the early 1990s in only two cohorts (table 5), statistically significant associations were found between NO₂ and both chronic bronchitis (OR: 1.10, 95% CI 1.00 to 1.22) and chronic cough (OR: 1.10, 95% CI 1.01 to 1.20).

DISCUSSION

This is one of the largest studies to investigate the link between bronchitis symptoms and current air pollution exposures using

five cohorts in nine European countries. Main analyses defined a priori did not show significant associations between the period prevalence of chronic bronchitis, cough or phlegm and any of six air pollutant metrics and two traffic indicators. Associations between the particulate measure of black carbon PM_{2.5abs} and chronic cough were statistically significant if leaving out a younger cohort (ECRHS) in analyses of all individuals and of never-smokers. In never-smokers, associations were in general larger and consistently positive, reaching statistical significance between phlegm and PM_{coarse} (but not PM_{2.5}). The higher NO₂ exposures in the early 1990s were associated with chronic bronchitis and cough, but this analysis was only possible for two cohorts.

Findings in comparisons with previous studies

To our knowledge, this is one of the first epidemiological studies to report on long-term associations between the coarse fraction of ambient particles and cough and phlegm in adults. PM_{coarse} has previously been found to be associated with respiratory hospital admissions³⁰ and to be more potent than fine PM in inducing inflammatory responses in in vitro and in vivo (mouse) studies.^{31 32}

We also observed significant associations between PM₁₀ and phlegm in never-smokers but not overall. As in this analysis, cross-sectional associations with chronic bronchitis and with phlegm were seen in never-smokers (but not in former and

Table 3 Never-smokers at the most recent assessment*: fixed-effect meta-analysis results on model 3 (adjusted for age, sex, smoking, education and season of interview) for all air pollutants and traffic indicators for each outcome, using ESCAPE-period (2008–2011) exposures from all five cohorts

Outcome	Chronic bronchitis		Chronic cough		Chronic phlegm	
	OR (95% CI)	P _{het} ‡	OR (95% CI)	P _{het}	OR (95% CI)	P _{het}
PM _{2.5} (5 µg/m ³)	1.28 (0.95 to 1.72)	0.488	1.11 (0.90 to 1.36)	0.091	1.16 (0.91 to 1.48)	0.519
PM _{2.5abs} (per 10 ⁻⁵ m ⁻¹)	1.20 (0.92 to 1.57)	0.233	1.16 (0.96 to 1.39)	0.032	1.10 (0.87 to 1.39)	0.602
PM ₁₀ (10 µg/m ³)	1.35 (0.97 to 1.88)	0.763	1.08 (0.86 to 1.35)	0.535	1.32 (1.02 to 1.71)	0.474
PM _{coarse} (5 µg/m ³)	1.15 (0.87 to 1.53)	0.979	1.06 (0.87 to 1.29)	0.954	1.31 (1.05 to 1.64)	0.457
NO ₂ (10 µg/m ³)	1.06 (0.93 to 1.20)	0.440	1.04 (0.97 to 1.12)	0.088	1.02 (0.92 to 1.13)	0.234
NO _x (20 µg/m ³)	1.09 (0.93 to 1.28)	0.151	1.04 (0.97 to 1.12)	0.021	1.05 (0.96 to 1.15)	0.121
Traffic intensity¶	1.12 (0.79 to 1.57)	0.763	1.07 (0.84 to 1.37)	0.629	1.04 (0.80 to 1.37)	0.830
Traffic load**	1.11 (0.83 to 1.49)	0.354	1.03 (0.82 to 1.29)	0.51	1.02 (0.79 to 1.32)	0.422

Bold type denotes statistical significance, $p < 0.05$.

*Asthma-E3N 2011, ECRHS 1998–2002, NSHD 2008, SALIA 2006–10, SAPALDIA 2002. Due to questionnaire wording SALIA (>70% never-smokers) is not included in analyses of phlegm alone.

†Estimates from random-effect meta-analysis as P_{het}: <0.05.

‡Results were interpreted as per exposure unit, as shown in the parentheses.

§P_{het}: P-value for heterogeneity.

¶Binary variable, <5000 (reference group) vs >5000 vehs/day.

**Binary variable, <500 000 (reference group) vs >500 000 vehs m/day.

ECRHS, European Community Respiratory Health Survey; ESCAPE, European Study of Cohorts for Air Pollution Effects; NO_x: nitrogen oxides; NSHD, National Survey of Health and Development; PM, particulate matter; SALIA, Study on the influence of Air pollution on Lung function, Inflammation and Aging; SAPALDIA, Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults.

current smokers) in the SAPALDIA study,²⁶ but no statistically significant associations were seen in SALIA (mainly non-smokers)²³ while continuous measures of PM₁₀ were not associated with cough in older adults in France.¹⁵ However, longitudinal analyses in both SALIA²² and SAPALDIA²⁴ studies suggested declines in PM₁₀ are associated with declines in cough and chronic bronchitis symptoms; additionally, an analysis of Seventh Day Adventist non-smokers found associations between chronic cough and 15-year cumulative PM₁₀ exposures.¹⁰

We saw no significant associations overall with PM_{2.5}. This is consistent with previous cross-sectional epidemiological studies in adults in the USA¹⁹ and a 2006 analysis of the ECRHS²⁵ cohort and with a longitudinal analysis in Melbourne¹⁴ but not an analysis in non-smoking Seventh Day Adventists, which found associations between 20-year cumulative exposure to PM_{2.5} and chronic bronchitis.¹¹ We did observe associations between chronic cough and PM_{2.5abs}, a measure of black carbon or soot, in some sensitivity analyses, but these were not consistent and may represent chance findings.

Lack of findings of significant associations with NO₂, except for chronic cough and chronic bronchitis in SALIA and SAPALDIA in the 1990s when exposures were higher are partially consistent with previous studies. Significant associations were seen with cough, but not chronic bronchitis in a previous analysis of SALIA²³; with chronic bronchitis and with phlegm in women but not men in the ECRHS (cough was not considered)²⁵; with phlegm (but not cough) in women but not men in an older French cohort¹⁵; and with chronic bronchitis and

chronic phlegm in never-smokers in SAPALDIA.²⁶ Chronic bronchitis symptoms were not associated with low levels of cumulative NO₂ exposure in non-smoking Californians.¹⁶

We are aware of only one adult study that has considered NO_x and contrary to our null findings, exposures >19 vs 0–8 µg/m³ in southern Sweden were associated with higher prevalences of chronic bronchitis.¹⁷

We found no significant associations of traffic intensity with any chronic bronchitis symptoms, contrary to six previous studies using differing traffic intensity metrics based on traffic counts^{17 23} and distance from road.^{13 20 21 27}

ORs using ESCAPE exposure estimates in individual cohorts were comparable with those from previously published analyses using cohort-specific air pollution estimates, allowing for differences in study design (see online supplements-11 for details).

Most^{10–13 15–17 19–21 23 25–27} but not all^{14 18 22 24} previous studies examining associations between air pollutant metrics and chronic bronchitis in adults have conducted cross-sectional analyses. We did not do a longitudinal analysis because symptoms come and go over time and they do not represent a stable chronic condition. Also, questionnaire-based reporting is most likely to capture symptoms experienced in the last few months, therefore reflecting cumulative prevalence of acute and subacute effects.

Strengths and weaknesses of the study

Strengths of this study are the use of five large existing cohorts in different parts of Europe, centrally defined harmonised

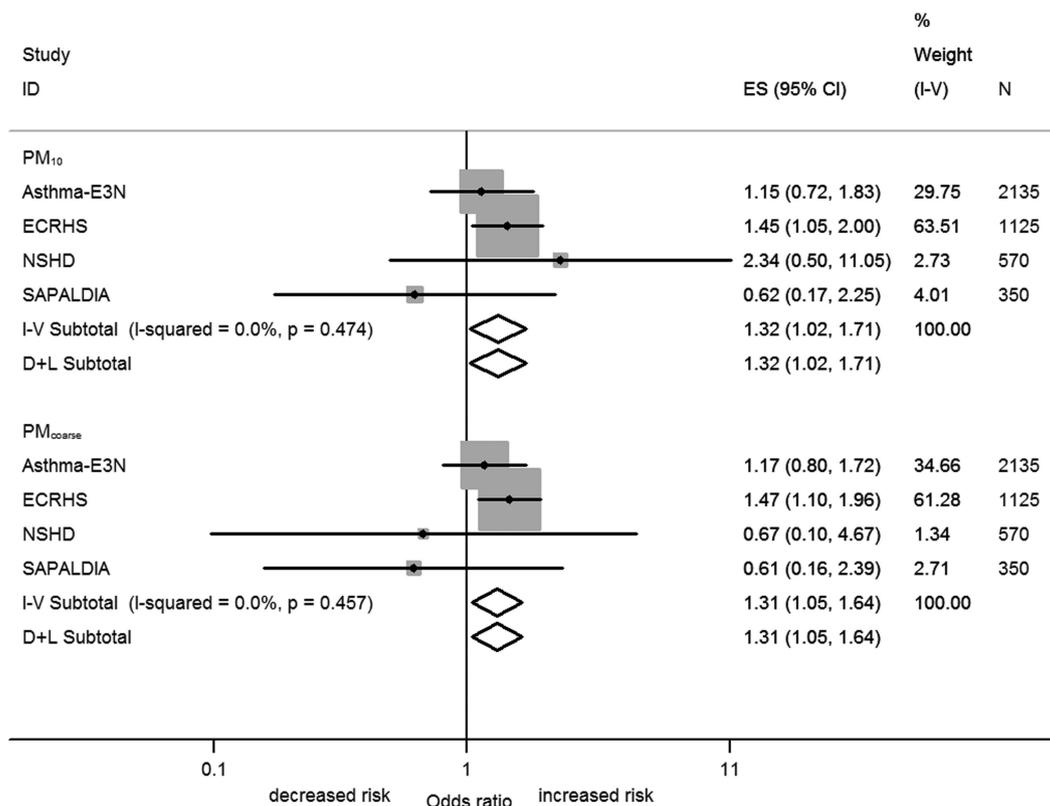


Figure 2 Meta-analysis results on model 3 (adjusted for age, sex, smoking, education, season of questionnaire interview) for PM₁₀ (per 10 µg/m³) and PM_{coarse} (per 5 µg/m³) for chronic phlegm at the most recent assessment using the European Study of Cohorts for Air Pollution Effects (ESCAPE)-period exposures in the never-smokers populations from four cohorts. I-squared, variation in estimated effect attributable to heterogeneity; I-V, inverse-variance weighted fixed effects method; D-L, DerSimonian-Laird random effects method; PM, particulate matter. The Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) was excluded from the above analysis because questions regarding phlegm production were not asked separately from cough. ES, effect estimate.

variables for each cohort, standard assessment of exposures to eight traffic-related exposures individually assigned to home address and an identical prespecified statistical protocol. However, there were also several limitations. First, uncertainty

in exposure estimates might have introduced non-systematic errors, reducing the power of the study to detect effects. However, analyses excluding models with spatial variation R² < 0.6 did not substantially change the results (online

Table 4 Back-extrapolated from ESCAPE-period exposures (2008–2011) to early 2000s 'historic exposure estimates': fixed-effect meta-analysis on cross-sectional results from ECRHS (2002), NSHD (1999), SAPALDIA (2002): all participants (upper section) and never-smokers (lower section), main model 3.

	Back-extrapolated NO ₂ , 10 µg/m ³					Back-extrapolated PM ₁₀ , 10 µg/m ³						
	Chronic bronchitis		Chronic cough		Chronic phlegm	Chronic bronchitis		Chronic cough		Chronic phlegm		
All participants	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cohort (year)												
ECRHS (2002)	0.99	(0.90 to 1.10)	1.03	(0.96 to 1.11)	1.01	(0.94 to 1.09)	1.22	(0.83 to 1.80)	1.03	(0.80 to 1.34)	1.29	(0.97 to 1.72)
NSHD (1999)	1.23	(0.99 to 1.54)	1.07	(0.91 to 1.27)	1.16	(0.96 to 1.41)	1.20	(0.57 to 2.53)	1.05	(0.61 to 1.79)	1.39	(0.74 to 2.61)
SAPALDIA (2002)	1.01	(0.77 to 1.33)	0.99	(0.71 to 1.40)	0.98	(0.84 to 1.15)	1.44	(0.63 to 3.28)	1.77	(0.65 to 4.86)	0.93	(0.59 to 1.45)
Overall effect	1.03	(0.94 to 1.12)	1.04	(0.97 to 1.11)	1.02	(0.96 to 1.09)	1.25	(0.91 to 1.71)	1.06	(0.85 to 1.34)	1.20	(0.96 to 1.50)
P _{het} :	0.213		0.897		0.350		0.932		0.596		0.420	
Never-smokers												
ECRHS (2002)	0.99	(0.79 to 1.23)	1.00	(0.91 to 1.10)	0.97	(0.83 to 1.14)	1.92	(0.92 to 3.99)	1.17	(0.74 to 1.84)	1.95	(1.09 to 3.49)
NSHD (1999)	1.04	(0.60 to 1.80)	0.97	(0.65 to 1.45)	0.84	(0.52 to 1.37)	1.45	(0.28 to 7.55)	0.71	(0.20 to 2.52)	1.00	(0.24 to 4.21)
SAPALDIA (2002)	0.92	(0.52 to 1.64)	0.70	(0.34 to 1.44)	0.88	(0.67 to 1.16)	0.65	(0.10 to 4.37)	0.59	(0.07 to 4.96)	0.77	(0.35 to 1.70)
Overall effect	0.99	(0.81 to 1.20)	0.99	(0.90 to 1.09)	0.94	(0.83 to 1.07)	1.63	(0.87 to 3.07)	1.08	(0.71 to 1.64)	1.37	(0.88 to 2.13)
P _{het} :	0.956		0.630		0.740		0.579		0.654		0.161	

P_{het}, p Value for heterogeneity.

ECRHS, European Community Respiratory Health Survey; ESCAPE, European Study of Cohorts for Air Pollution Effects; NSHD, National Survey of Health and Development; PM, particulate matter; SAPALDIA, Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults.

Table 5 Back-extrapolated from ESCAPE-period exposures (2008–11) to early 1990s 'historic exposure estimates': fixed-effect meta-analysis on cross-sectional results from SALIA (1985–1994), SAPALDIA (1991): all participants (upper section) and never-smokers (lower section), main model 3.

All participants	Back-extrapolated NO ₂ , 10 µg/m ³				Back-extrapolated PM ₁₀ , 10 µg/m ³			
	Chronic bronchitis		Chronic cough		Chronic bronchitis		Chronic cough	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cohort (year)								
SALIA (1985–94)	1.08	(0.96 to 1.21)	1.08	(0.98 to 1.20)	1.04	(0.85 to 1.29)	1.10	(0.92 to 1.33)
SAPALDIA (1991)	1.17	(0.96 to 1.44)	1.17	(0.96 to 1.42)	1.19	(0.49 to 2.91)	1.16	(0.48 to 2.79)
Overall effect	1.10	(1.00 to 1.22)	1.10	(1.01 to 1.20)	1.05	(0.86 to 1.29)	1.11	(0.92 to 1.33)
P _{het} :	0.474		0.510		0.776		0.909	
Never-smokers								
SALIA (1985–94)	1.09	(0.94 to 1.26)	1.03	(0.91 to 1.17)	1.04	(0.80 to 1.35)	1.02	(0.81 to 1.27)
SAPALDIA (1991)	1.24	(0.85 to 1.79)	1.25	(0.86 to 1.80)	0.90	(0.19 to 4.30)	0.81	(0.17 to 3.77)
Overall effect	1.11	(0.97 to 1.27)	1.05	(0.93 to 1.18)	1.04	(0.80 to 1.34)	1.01	(0.81 to 1.26)
P _{het} :	0.538		0.330		0.858		0.774	

Bold type denotes statistical significance, $p < 0.05$.

P_{het}, p Value for heterogeneity.

Only outcomes available for both SALIA and SAPALDIA are included—analyses of phlegm alone could not be conducted in SALIA due to questionnaire wording.

ESCAPE, European Study of Cohorts for Air Pollution Effects; PM, particulate matter; SALIA, Study on the influence of Air pollution on Lung function, Inflammation and Aging;

SAPALDIA, Swiss cohort study on Air Pollution And Lung and heart Diseases in Adults.

supplements-10 and supplements-12) Second, exposure assessments for ESCAPE occurred years after questionnaire assessments in some cohorts. This was investigated using back-extrapolated exposure assessments aligned with questionnaire. Back-extrapolation assumes within-city spatial contrasts of air pollutants remain similar over long periods of time, for which there is some support from previous studies.^{33 34} Third, harmonised information on confounders was limited. Fourth, there might be reporting bias, particularly reluctance to report phlegm in females.³⁵ Fifth, we conducted many statistical analyses and it is possible that observed associations were due to chance. Sixth, the cohorts were heterogeneous in both design and populations, which may have resulted in systematic differences between studies. To address this, we used harmonised variables, explored potential effect modifiers, used meta-analyses not pooled analyses and conducted leave-one-out sensitivity meta-analyses. Finally, we note that detecting effects in potentially susceptible subgroups, of relevance to environmental policy, may require much larger sample sizes than possible here.

In conclusion, although deleterious effects of ambient air pollution on a range of health outcomes including mortality are well documented, we did not find evidence for significant associations between current long-term average air pollution levels and symptoms of chronic bronchitis, cough or phlegm in >10 000 European adults. Our study findings, based on very large-scale harmonised population-based cohort studies using *a priori* specified analyses, contribute to strengthening the evidence-based studies for policy formulation.

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Acknowledgements We thank all study members and staff involved in data collections in each cohort.

E3N We wish to thank all the women from the E3N study. We also thank Lyan Hoang, Maryvonne Niravong and Marie Fangon for invaluable assistance with the implementation of the study.

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, EH Walters, F Thien), Belgium: South Antwerp & Antwerp City (P Vermeire⁺, J Weyler, M Van Sprundel, V Nelen), Denmark: Aarhus (EJ 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 Picci oni, E Caria, A Carosso, E Migliore, G Castiglioni), Verona (R de Marco, G Ver lato, E Zanolini, 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), Netherlands: Groningen & Geleen (J Schouten, M Kerkhof), Norway: Bergen (A Gulsvik, E Omenaas, C Svanes, B Laerum), Spain: Barcelona (JM Anto, J Sunyer, M Kogevinas, JP Zock, X Basagana, A Jaen, F Burgos), Huelva (J Maldonado, A Pereira, JL 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, AC 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).

[†]Deceased

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

SALIA During the last decades, a lot of 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 organizing the baseline study and Barbara Schulten as study nurse for her help in organizing the follow-up study. We are most grateful for all the women from the Ruhr area and from Borcken who participated in the study during decades.

SAPALDIA *Study directorate:* T Rochat (p), NM Probst Hensch (e/g), JM Gaspoz (c), N Künzli (e/exp), C Schindler(s).

Scientific team: JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), G Bolognini (p), O Brändli (p), C Brombach (n), M Brutsche (p), L Burdet (p), M Frey (p), U Frey (pd), MW Gerbase (p), D Gold (e/c/p), E de Groot (c), W Karrer (p), R Keller (p), B Knöpfli (p), B Martin (pa), D Miedinger (o), U Neu (exp), L Nicod (p), M Pons (p), F Roche (c), T Rothe (p), E Russi (p), P Schmid-Grendelmeyer (a), A Schmidt-Trucksäss (pa), A Turk (p), J Schwartz (e), D. Stolz (p), P Straehl (exp), JM Tschopp (p), A von Eckardstein (cc), E Zemp Stutz (e).

Scientific team at coordinating centres: M Adam (e/g), E Boes (g), PO Bridevaux (p), D Carballo (c), E Corradi (e), I Curjuric (e), J Dratva (e), A Di Pasquale (s), L Grize (s), D Keidel (s), S Kriemler (pa), A Kumar (g), M Imboden (g), N Maire (s), A Mehta (e), F Meier (e), H Phuleria (exp), E Schaffner (s), GA Thun (g) A Ineichen (exp), M Ragettli (e), M Ritter (exp), T Schikowski (e), G Stern (pd), M Tarantino (s), M Tsai (e), M Wanner (pa)

(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) paediatrics, (s) statistics

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 Bürlin, 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, MT Mandia, G Solari, B Viscardi, Montana: AP 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.

Contributors Conceptualised the study: ALH, YC, ZA-K, MA and the Steering Committee of ESCAPE WP4: NP-H, FK, UK, TS, JS, NK (Chair). Drafted and edited the paper: YC, ALH, TS, NK. Discussed and interpreted the findings: ESCAPE WP4 working group: MA, AB, A-EC, YC, ALH, NP-H, BJ, FK, NK, UK, AM, JS, MS, TS, AV. Cohort data collections: MB, FC-C, BF, MWG, JH, NP-H, RH, DJ, FK, DKU, NK, UK, TR, CS, JS, ST, AV, RV. Air pollution assessments: RB, BB, MC, AdN, CD, KdH, REDS, VVF, GH, MJN, AR, MSR, DS, MT. Statistical analysis: ZAK, MA, AB, A-EC, YC, BJ, DKei, AM, CS, MS, TS, AV. All authors have revised the paper and approved the final version.

Funding 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.

E3N cohort is being studied with the financial support of the Mutuelle générale de l'éducation nationale, the European Community, the Ligue nationale contre le cancer, the Institut Gustave-Roussy, INSERM, and a grant from the World Cancer Research Fund (grant no. 2007/14). The Asthma-E3N study was supported by the Fonds de dotation 'Recherche en Santé Respiratoire'.

ECRHS was supported by the European Commission, as part of their Quality of Life programme.

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 of Epidemiology and Public Health has been established and founded by Instituto de Salud Carlos III.

Erfurt—GSF—National Research Centre for Environment & Health, Deutsche Forschungsgemeinschaft (DFG) (grant code FR 1526/1-1), funded by Helmholtz Zentrum Munich and grants from the German Research Foundation (HE3294/10-1).

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 Solidarité, 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 Solidarité, 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.

Pavia—Glaxo, Smith & Kline Italy, Italian Ministry of University and Scientific and Technological Research (MURST), Local University Funding for Research 1998 & 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 & Allergy Research, Swedish Asthma & Allergy Foundation, Västerbotten County Council (ALF).

Verona—University of Verona; Italian Ministry of University and Scientific and Technological Research (MURST); Glaxo, Smith & Kline Italy.

NSHD, the National Survey of Health and Development was funded by the UK Medical Research Council (MRC). The NSHD and Professors Hardy and Kuh are supported by core funding and grant funding (MC_UU_12019/1, MC_UU_12019/2, MC_UU_12019/4) from the UK Medical Research Council.

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 33CSGO-134276/1, 33CSGO-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; The Swiss National Science Foundation and German research Foundation D-A-CH grant no 32473BM-133148.

Measurements and models for PM in Grenoble (ECRHS) were funded by Region Rhône-Alpes.

Ethics approval Ethical approval was obtained for each of five participating cohorts in this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The ESCAPE air pollution data are available for use in future research projects on application to the ESCAPE steering committee (PI Burt Brunekreef).

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