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

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**Summary Box**

- **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 $NO_2$.

# 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 ($PM_{10}$, $PM_{2.5}$, $PM_{absorbance}$, $PM_{coarse}$), $NO_2$, $NO_x$ and road traffic measures modelled from ESCAPE measurement campaigns 2008-11 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:** 15279 and 10537 participants respectively were included in the main $NO_2$ 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 $NO_2$ and $PM_{10}$ 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 (1.05-1.64) per 5 $\mu g/m^3$ increase and $PM_{10}$ 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.

## 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 phlegm[2] and cough[3] have been considered separately and may have differing mechanisms – for example, cough may result from central reflex sensitivity[4] 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 COPD patients, 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 (e.g. distance from the main road[13,20,21,27], traffic intensity[17]),  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 ESCAPE (European Study of Cohorts for Air Pollution Effects) 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 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 three 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 ($NO_2$) and nitrogen oxides ($NO_X$) measurements were conducted in 36 ESCAPE study areas while PM ($PM_{10}$, particulate matter with aerodynamic diameter ≤10μm & $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5μm) 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 metre buffer (*Traffic load*, vehicles*m/day).

Each participant was assigned an annual average concentration at home outdoor of $NO_2$, $NO_X$ and the background levels of $NO_2$. For participants residing within ESCAPE areas with PM measurements, they were also assigned exposures to $PM_{2.5}$, $PM_{10}$, the coarse fraction of PM ($PM_{coarse}$ as $PM_{10}$ 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 2008-11, 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 pre-defined back-extrapolation algorithm (see http://www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf accessed 10 May 2014).

Back-extrapolation for $NO_2$ and $PM_{10}$ 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 1985-94, 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 Odds Ratios (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-value<0.05) existed across cohorts.

The main analyses used '**ESCAPE-period exposure**' for 2008-11 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 indicators 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 (Chronic Obstructive Pulmonary Disease) 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-value<0.05) existed across cohorts. Results presented/used in the meta-analyses for multi-country 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 2008-11 estimates for Asthma-E3N (2011), NSHD (2008) and SALIA (2006/10) i.e. 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 1985-94) i.e. when exposures were higher.


Statistical analyses were performed using Stata 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 15279 participants successfully assigned at least $NO_2$ estimates (**Table 1**) and 10537 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) (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 $\mu g/m^3$ (NSHD) to 31 $\mu g/m^3$ (Asthma-E3N) whereas mean $PM_{10}$ ranged from 16 $\mu g/m^3$ (NSHD) to 27 $\mu g/m^3$ (SALIA).  Within-study contrasts assessed by IQR varied from 8 $\mu g/m^3$ in SAPALDIA to 20 $\mu g/m^3$ in ECRHS for $NO_2$ and2 $\mu g/m^3$ (NSHD) to 9.2 $\mu g/m^3$ (ECRHS) for $PM_{10}$. Exposures back-extrapolated to the 1990s   were higher than for estimates at later assessments.

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

ESCAPE-period exposures estimates 2008-11 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 (2006-10) (online supplements-9), were all null except for associations between chronic cough and $PM_{2.5abs}$ in analyses not including ECRHS, with OR, 95%CI 1.20 (1.01-1.44) per $10^{-5}/m$.

Further adjustments in Model 4 and 5 did not change the results substantially, although   effect estimates were slightly smaller and the 95% confidence intervals (CI) 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(1.02-1.71), per 10 $\mu g/m^3$ increase) and $PM_{coarse}$ (OR, 95%CI: 1.31(1.05-1.64), per 5 $\mu g/m^3$ 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 $PM_{2.5}$ and $PM_{2.5abs}$ became larger and statistically significant: $PM_{2.5}$ OR, 95%CI: 1.47 (1.02-2.12) per 5 μg/m$^3$ increase, $PM_{2.5abs}$ OR, 95%CI: 1.30 (1.04-1.63) per 10$^{-5}$/m, albeit with evidence of heterogeneity for the latter ($P_{het}$=0.024). In the random-effects analysis, the $PM_{2.5abs}$ result was not statistically significant: OR, 95%CI 1.58 (0.90-2.76) 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 $NO_2$ and $NO_x$ excluding centres with LUR model validation $R^2$ statistics<0.6 gave similar null results for the main ESCAPE-period analyses (online supplements-10). The $R^2$ 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 $NO_2$ and $PM_{10}$. 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: 1.00-1.22) and chronic cough (OR: 1.10, 95%CI: 1.01-1.20).


## 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 $NO_2$ 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 admissions[30] 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 $PM_{10}$ 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 current smokers) in the SAPALDIA study[26], but no statistically significant associations were seen in SALIA (mainly non-smokers)[23] while continuous measures of $PM_{10}$ were not associated with cough in older adults in France[15]. However, longitudinal analyses in both SALIA[22] and SAPALDIA[24] studies suggested declines in $PM_{10}$ 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 $PM_{10}$ 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 USA[19] and a 2006 analysis of the ECRHS[25] cohort and with a longitudinal analysis in Melbourne[14]but not an analysis in non-smoking Seventh Day Adventists found associations between 20 year cumulative exposure to $PM_{2.5}$ and chronic bronchitis[11]. We did observe associations between chronic cough and PM2.5abs, 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 $NO_2$, except for chronic cough and chronic bronchitis in (SALIA and SAPALDIA) 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 SALIA[23]; 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 cohort[15]; and with chronic bronchitis and chronic phlegm in never smokers in SAPALDIA[26]. Chronic bronchitis symptoms were not associated with low levels of cumulative $NO_2$ exposure in non-smoking Californians[16].

We are aware of only one adult study that has considered NOx and contrary to our null findings, exposures >19 vs. 0-8 $\mu g/m^3$ 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].

Odds ratios 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 sub-acute 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 variables for each cohort, standard assessment of exposures to eight traffic-related exposures individually-assigned to home address and an identical pre-specified statistical protocol. However, there were also several limitations. Firstly,  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 supplements-10 and supplements-12) Secondly, 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]. Thirdly, harmonised information on confounders was

limited. Fourthly, there might be reporting bias, particularly reluctance to report phlegm in females[35]. Fifthly, we conducted many statistical analyses and it is possible that observed associations were due to chance. Sixthly, 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 potential 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 for policy formulation.

Table **1** Description of study population (sub-populations of the original study with individually assigned NO$_2$ measures) of all five cohorts as used at each assessment. The table shows the N (and % of N) for categorical variables and Mean (standard deviation,SD) for continuous variables.

| Study | Asthma-E3N | | ECRHS | | NSHD | | | | SALIA | | | | SAPALDIA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Co-variables | 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% |

*ETS = Environmmental Tobacco Smoke at home and/or at work ; VGDF = occupational vapour/gases/dust/fumes exposure(any of).*
*\*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 coho*

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 | Chronic bronchitis | | Chronic cough | | Chronic phlegm | |
|---|---|---|---|---|---|---|
| Exposure[1] | OR (95%CI) | $P_{het}$ [2] | OR (95%CI) | $P_{het}$ | OR (95%CI) | $P_{het}$ |
| $PM_{2.5}$, (5$\mu$g/m$^3$) | 0.90 (0.74-1.09) | 0.754 | 0.91 (0.80-1.04) | 0.440 | 0.96 (0.84-1.11) | 0.850 |
| $PM_{2.5abs}$, (per 10$^{-5}$*m$^{-1}$) | 1.02 (0.85-1.22) | 0.504 | 1.01 (0.89-1.15) | 0.070 | 1.02 (0.88-1.18) | 0.693 |
| $PM_{10}$, (10$\mu$g/m$^3$) | 0.92 (0.75-1.13) | 0.193 | 0.92 (0.80-1.06) | 0.494 | 1.02 (0.87-1.18) | 0.696 |
| PMcoarse, (5$\mu$g/m$^3$) | 0.99 (0.83-1.18) | 0.165 | 0.99 (0.87-1.12) | 0.737 | 1.07 (0.94-1.22) | 0.131 |
| $NO_2$, (10$\mu$g/m$^3$) | 1.00 (0.92-1.08) | 0.973 | 1.05 (0.99-1.11) | 0.953 | 1.01 (0.95-1.07) | 0.656 |
| $NO_x$, (20$\mu$g/m$^3$) | 1.02 (0.94-1.09) | 0.793 | 1.04 (0.98-1.09) | 0.622 | 1.02 (0.96-1.08) | 0.393 |
| Traffic intensity[3] | 0.95 (0.75-1.19) | 0.739 | 0.96 (0.80-1.14) | 0.339 | 0.98 (0.82-1.17) | 0.366 |
| Traffic Load[4] | 0.99 (0.82-1.20) | 0.509 | 0.95 (0.81-1.10) | 0.831 | 0.97 (0.83-1.13) | 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.

[1]: Results were interpreted as per Exposure unit, as shown in the bracket.

[2]: $P_{het}$: P-value for heterogeneity.

[3]: Binary variable, <5,000 (reference group) vs. >5,000 vehs/day.

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

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 | |
|---|---|---|---|---|---|---|
| Exposure[1] | OR (95%CI) | $P_{het}$ [2] | OR (95%CI) | $P_{het}$ | OR (95%CI) | $P_{het}$ |
| $PM_{2.5}$ , (5µg/m³) | 1.28 (0.95-1.72) | 0.488 | 1.11 (0.90-1.36) | 0.091 | 1.16 (0.91-1.48) | 0.519 |
| $PM_{2.5abs}$, (per $10^{-5}*m^{-1}$) | 1.20 (0.92-1.57) | 0.233 | 1.16 (0.96-1.39) 1.27ɫ (0.88-1.85) | 0.032 | 1.10 (0.87-1.39) | 0.602 |
| $PM_{10}$, (10µg/m³) | 1.35 (0.97-1.88) | 0.763 | 1.08 (0.86-1.35) | 0.535 | **1.32 (1.02-1.71)** | 0.474 |
| PMcoarse, (5µg/m³) | 1.15 (0.87-1.53) | 0.979 | 1.06 (0.87-1.29) | 0.954 | **1.31 (1.05-1.64)** | 0.457 |
| $NO_2$, (10µg/m³) | 1.06 (0.93-1.20) | 0.440 | 1.04 (0.97-1.12) | 0.088 | 1.02 (0.92-1.13) | 0.234 |
| NOx , (20µg/m³) | 1.09 (0.93-1.28) | 0.151 | 1.04 (0.97-1.12) 1.06ɫ (0.91-1.23) | 0.021 | 1.05 (0.96-1.15) | 0.121 |
| Traffic intensity[3] | 1.12 (0.79-1.57) | 0.763 | 1.07 (0.84-1.37) | 0.629 | 1.04 (0.80-1.37) | 0.830 |
| Traffic Load[4] | 1.11 (0.83-1.49) | 0.354 | 1.03 (0.82-1.29) | 0.51 | 1.02 (0.79-1.32) | 0.422 |

* 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.

ɫ Estimates from random-effect meta-analysis as $P_{het:}$ <0.05

[1]: Results were interpreted as per Exposure unit, as shown in the bracket.

[2]: $P_{het:}$ P-value for heterogeneity.

[3]: Binary variable, <5,000 (reference group) vs. >5,000 vehs/day.

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

**Table 4**: Back-extrapolated from ESCAPE-period exposures (2008-11) 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.

| All participants | back-extrapolated $NO_2$, 10 µg/m³ | | | | | | back-extrapolated $PM_{10}$, 10µg/m³ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chronic bronchitis | | Chronic cough | | Chronic phlegm | | Chronic bronchitis | | Chronic cough | | Chronic phlegm | |
| Cohort(year) | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| ECRHS(2002) | 0.99 | (0.90-1.10) | 1.03 | (0.96-1.11) | 1.01 | (0.94-1.09) | 1.22 | (0.83-1.80) | 1.03 | (0.80-1.34) | 1.29 | (0.97-1.72) |
| NSHD(1999) | 1.23 | (0.99-1.54) | 1.07 | (0.91-1.27) | 1.16 | (0.96-1.41) | 1.20 | (0.57-2.53) | 1.05 | (0.61-1.79) | 1.39 | (0.74-2.61) |
| SAPALDIA(2002) | 1.01 | (0.77-1.33) | 0.99 | (0.71-1.40) | 0.98 | (0.84-1.15) | 1.44 | (0.63-3.28) | 1.77 | (0.65-4.86) | 0.93 | (0.59-1.45) |
| Overall effect | 1.03 | (0.94-1.12) | 1.04 | (0.97-1.11) | 1.02 | (0.96-1.09) | 1.25 | (0.91-1.71) | 1.06 | (0.85-1.34) | 1.20 | (0.96-1.50) |
| $P_{het}$: | 0.213 | | 0.897 | | 0.350 | | 0.932 | | 0.596 | | 0.420 | |
| **Never-smokers** | | | | | | | | | | | | |
| ECRHS(2002) | 0.99 | (0.79-1.23) | 1.00 | (0.91-1.10) | 0.97 | (0.83-1.14) | 1.92 | (0.92-3.99) | 1.17 | (0.74-1.84) | 1.95 | (1.09-3.49) |
| NSHD(1999) | 1.04 | (0.60-1.80) | 0.97 | (0.65-1.45) | 0.84 | (0.52-1.37) | 1.45 | (0.28-7.55) | 0.71 | (0.20-2.52) | 1.00 | (0.24-4.21) |
| SAPALDIA(2002) | 0.92 | (0.52-1.64) | 0.70 | (0.34-1.44) | 0.88 | (0.67-1.16) | 0.65 | (0.10-4.37) | 0.59 | (0.07-4.96) | 0.77 | (0.35-1.70) |
| Overall effect | 0.99 | (0.81-1.20) | 0.99 | (0.90-1.09) | 0.94 | (0.83-1.07) | 1.63 | (0.87-3.07) | 1.08 | (0.71-1.64) | 1.37 | (0.88-2.13) |
| $P_{het}$: | 0.956 | | 0.630 | | 0.740 | | 0.579 | | 0.654 | | 0.161 | |

$P_{het}$: P-value for heterogeneity

**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 (1985-94), SAPALDIA (1991): all participants (upper section) and never-smokers (lower section), Main model 3.

| all participants | back-extrapolated $NO_2$, 10µg/m$^3$ | | | | back-extrapolated $PM_{10}$, 10µg/m$^3$ | | | |
|---|---|---|---|---|---|---|---|---|
| | Chronic bronchitis | | Chronic cough | | Chronic bronchitis | | Chronic cough | |
| Cohort(year) | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| SALIA(1985-94) | 1.08 | (0.96-1.21) | 1.08 | (0.98-1.20) | 1.04 | (0.85-1.29) | 1.10 | (0.92-1.33) |
| SAPALDIA(1991) | 1.17 | (0.96-1.44) | 1.17 | (0.96-1.42) | 1.19 | (0.49-2.91) | 1.16 | (0.48-2.79) |
| Overall effect | **1.10** | **(1.00-1.22)** | **1.10** | **(1.01-1.20)** | 1.05 | (0.86-1.29) | 1.11 | (0.92-1.33) |
| $P_{het}$: | 0.474 | | 0.510 | | 0.776 | | 0.909 | |
| **Never-smokers** | | | | | | | | |
| SALIA(1985-94) | 1.09 | (0.94-1.26) | 1.03 | (0.91-1.17) | 1.04 | (0.80-1.35) | 1.02 | (0.81-1.27) |
| SAPALDIA(1991) | 1.24 | (0.85-1.79) | 1.25 | (0.86-1.80) | 0.90 | (0.19-4.30) | 0.81 | (0.17-3.77) |
| Overall effect | 1.11 | (0.97-1.27) | 1.05 | (0.93-1.18) | 1.04 | (0.80-1.34) | 1.01 | (0.81-1.26) |
| $P_{het}$: | 0.538 | | 0.330 | | 0.858 | | 0.774 | |

$P_{het}$: 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.

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**The authors declare that they have no conflict of interest.**

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## Figures legends

Figure **1** Meta-analysis results on Model 3 (adjusted for age, sex, smoking, education, season of questionnaire interview) for $NO_2$ (per 10 µg/m$^3$) ,$PM_{10}$ (per 10 µg/m$^3$) and $PM_{2.5abs}$ (per $10^{-5}$*m$^{-1}$)  for **chronic cough** at the most recent assessment using the ESCAPE-period exposures   in the **overall** populations from all five cohorts.
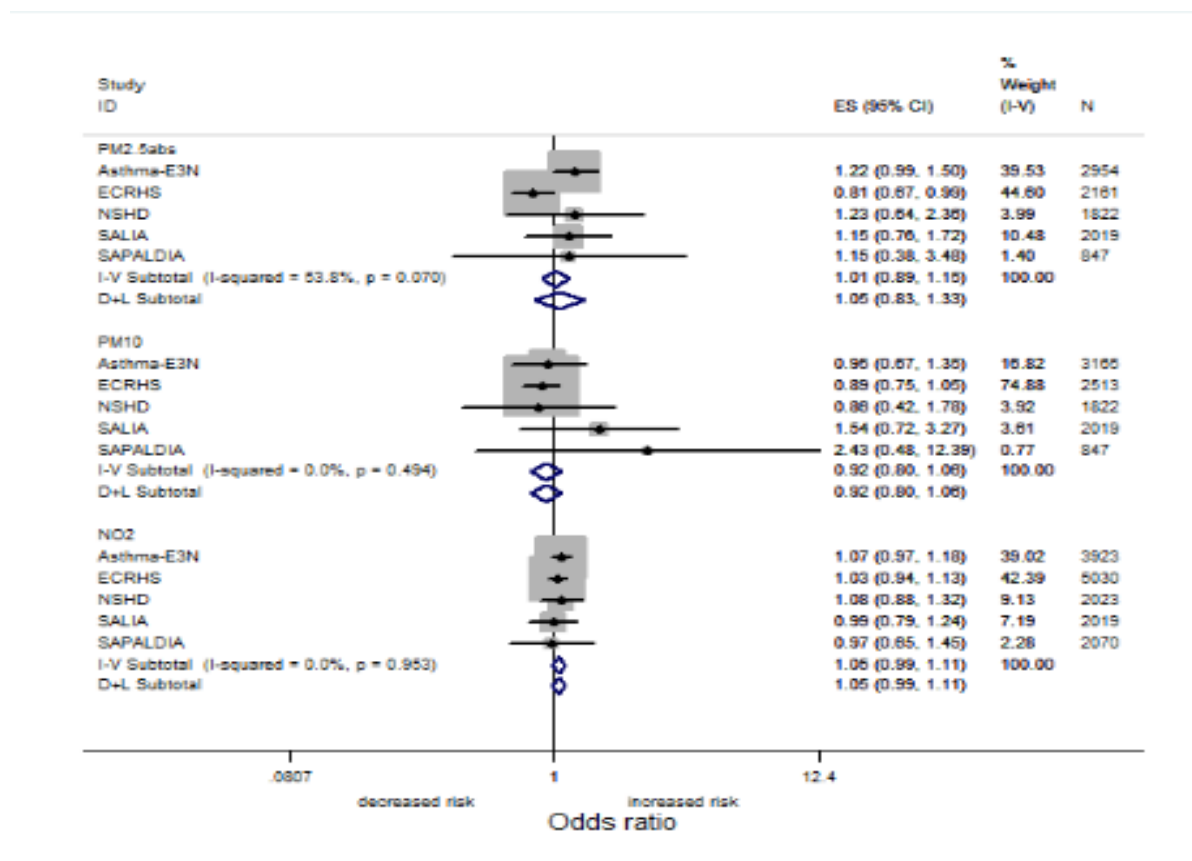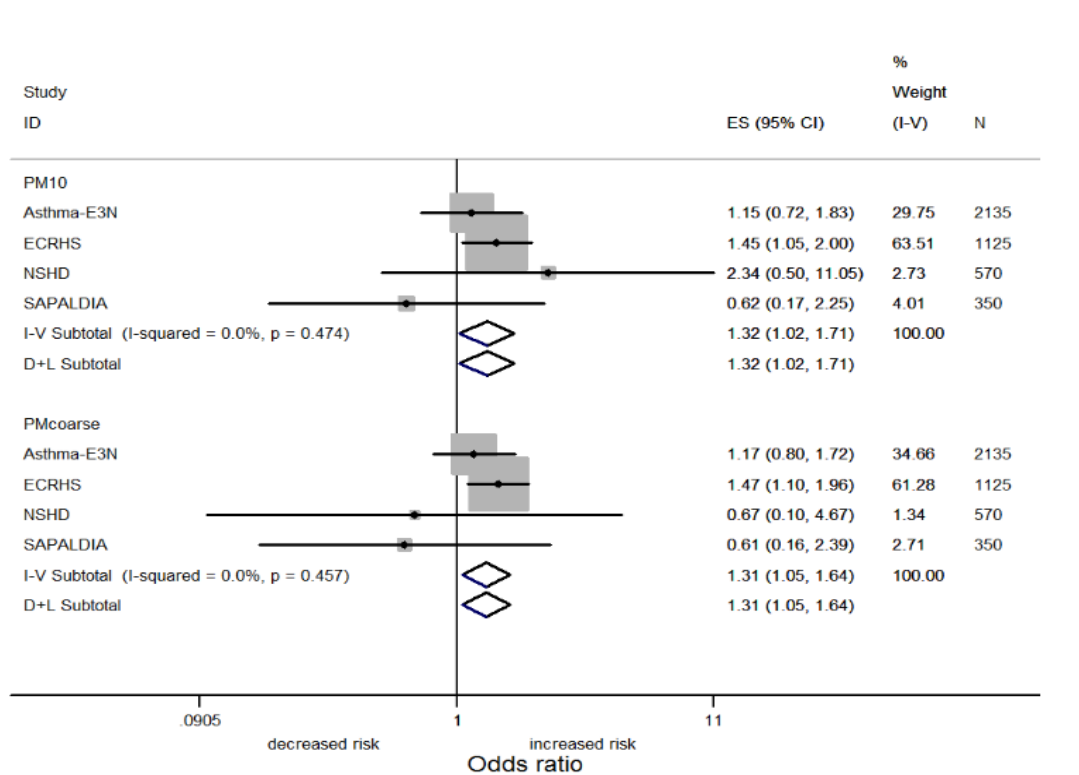


*I-squared*: variation in estimated effect attributable to heterogeneity
*I-V*: Inverse-Variance weighted fixed effects method
*D-L*: DerSimonian-Laird random effects method

Figure **2** Meta-analysis results on Model 3 (adjusted for age, sex, smoking, education, season of questionnaire interview) for PM$_{10}$ (per 10 μg/m$^3$) and PMcoarse (per 5 μg/m$^3$) for **chronic phlegm** at the most recent assessment using the 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
*The SALIA study was excluded from the above analysis because questions regarding phlegm production were not asked separately from cough*