Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

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Summary

Background Ambient air pollution is suspected to cause lung cancer. We aimed to assess the association between long-term exposure to ambient air pollution and lung cancer incidence in European populations.

Methods This prospective analysis of data obtained by the European Study of Cohorts for Air Pollution Effects used data from 17 cohort studies based in nine European countries. Baseline addresses were geocoded and we assessed air pollution by land-use regression models for particulate matter (PM) with diameter of less than 10 μm (PM_{10}), less than 2·5 μm ($PM_{2·5}$), and between 2·5 and 10 μm (PM_{coarse}), soot ($PM_{2·5absorbance}$), nitrogen oxides, and two traffic indicators. We used Cox regression models with adjustment for potential confounders for cohort-specific analyses and random effects models for meta-analyses.

Findings The 312 944 cohort members contributed 4 013 131 person-years at risk. During follow-up (mean 12·8 years), 2095 incident lung cancer cases were diagnosed. The meta-analyses showed a statistically significant association between risk for lung cancer and PM_{10} (hazard ratio [HR] 1·22 [95% CI 1·03–1·45] per 10 μg/m³). For $PM_{2·5}$ the HR was 1·18 (0·96–1·46) per 5 μg/m³. The same increments of PM_{10} and $PM_{2·5}$ were associated with HRs for adenocarcinomas of the lung of 1·51 (1·10–2·08) and 1·55 (1·05–2·29), respectively. An increase in road traffic of 4000 vehicle-km per day within 100 m of the residence was associated with an HR for lung cancer of 1·09 (0·99–1·21). The results showed no association between lung cancer and nitrogen oxides concentration (HR 1·01 [0·95–1·07] per 20 μg/m³) or traffic intensity on the nearest street (HR 1·00 [0·97–1·04] per 5000 vehicles per day).

Interpretation Particulate matter air pollution contributes to lung cancer incidence in Europe.

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Introduction

Lung cancer is one of the most common cancers and has a poor prognosis. Active smoking is the main cause, but occupational exposures, residential radon, and environmental tobacco smoke are also established risk factors. Furthermore, lower socioeconomic position has been associated with a higher risk for lung cancer.[1] Ambient air pollution, specifically particulate matter with absorbed polycyclic aromatic hydrocarbons and other genotoxic chemicals, is suspected to increase the risk for lung cancer. Results of several epidemiological studies have shown higher risks for lung cancer in association with various measures of air pollution[2–11] and suggested an association mainly in non-smokers[4,12] and never-smokers[13,14] and in individuals with low fruit consumption.[4,13] In developed countries, overall lung cancer incidence rates have stabilised during the past few decades, but major shifts have been recorded in the frequencies of different histological types of lung cancer, with substantial relative increases in adenocarcinomas and decreases in squamous-cell carcinomas.[15] Changes in tobacco blends[15] and ambient air pollution[16,17] might have contributed to these shifts.

Within the European Study of Cohorts for Air Pollution Effects (ESCAPE), we aimed to analyse data from 17 European cohort studies with a wide range of exposure levels to investigate the following hypotheses: that ambient air pollution at the residence (specifically particulate matter) is associated with risk for lung cancer; that the association between air pollution and risk for lung cancer is stronger for non-smokers and people with low fruit intake; and that the association with air pollution is stronger for adenocarcinomas and squamous-cell carcinomas than for all lung cancers combined.

Methods

Study design and participants

This study is a prospective analysis of data obtained by ESCAPE—an investigation into the long-term effects of

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exposure to air pollution on human health in Europe—which included 36 European areas in which air pollution was measured, land-use regression models were developed, and cohort studies were located. The present study included 17 cohort studies, located in 12 areas, from which information about incident lung cancer cases and the most important potential confounders could be obtained, and where the resources needed for participation were available. These cohorts were in Sweden (European Prospective Investigation into Cancer and Nutrition [EPIC]-Umeå, Swedish National Study on Aging and Care in Kungsholmen [SNAC-K], Stockholm Screening Across the Lifespan Twin study and TwinGene [SALT], Stockholm 60 years old and IMPROVE study [Sixty], Stockholm Diabetes Prevention Program [SDPP]), Norway (Oslo Health Study [HUBRO]), Denmark (Diet, Cancer and Health study [DCH]), the Netherlands (EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [MORGEN], EPIC-PROSPECT), the UK (EPIC-Oxford), Austria (Vorarlberg Health Monitoring and

Prevention Programme [VHM&PP]), Italy (EPIC-Varese, EPIC-Turin, Italian Studies of Respiratory Disorders in Childhood and Environment [SIDRIA]-Turin, SIDRIA-Rome), Spain (EPIC-San Sebastian), and Greece (EPIC-Athens; figure 1). The study areas were mostly large cities and the surrounding suburban or rural communities. Some of the cohorts covered large regions of the country, such as EPIC-MORGEN in the Netherlands, EPIC-Oxford in the UK, and the VHM&PP cohort in Austria. For DCH, EPIC-Oxford, VHM&PP, and EPIC-Athens, exposure to air pollution was assessed for part of the original cohort only, and only those parts were analysed (restrictions are specified in the appendix pp 8, 11, 12, and 18). The use of cohort data in ESCAPE was approved by the local ethical and data protection authorities. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Procedures

The association between long-term exposure to air pollution and incidence of lung cancer was analysed in each cohort separately at the local centre by common standardised protocols for exposure assessment, outcome definition, confounder models, and statistical analyses. Cohort-specific effect estimates were combined by meta-analysis at the Danish Cancer Society Research Center, Copenhagen, Denmark. A pooled analysis of all cohort data was not possible due to data transfer and privacy issues.

The main outcome was all cancers of the lung; secondary analyses addressed adenocarcinomas and squamous-cell carcinomas of the lung. We included cancers located in the bronchus and the lung (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD10] and International Classification of Diseases for Oncology, 3rd edition [ICDO3] C34·0–C34·9). We only included primary cancers (ie, not metastases). Each cancer was histologically characterised, and data for squamous-cell carcinomas (ICDO3 8050–8084; fifth digit morphology code 3) and adenocarcinomas (ICDO3 8140–8384; fifth digit morphology code 3) in particular were obtained. Lymphomas in the lung (ICDO3 morphology codes 9590/3–9729/3) were not included. The characterisation of histology was based on routine pathology; this study did not include verification of tumour histology. The cohort members were followed up for cancer incidence in national or local cancer registries, except for EPIC-Athens, in which cancer cases were identified by questionnaires and telephone interviews followed by verification of medical records, and the SIDRIA cohorts, for which hospital discharge and mortality register data were used.

Exposure assessment

Air pollution concentrations at the baseline residential addresses of study participants were estimated by land-use regression models in a three-step, standardised

Figure 1: Areas where cohort members lived, measurements were taken, and land-use regression models for prediction of air pollution were developed

NO_2=nitrogen dioxide. NOx=nitrogen oxides (the sum of nitric oxide and nitrogen dioxide). PM=particulate matter.

procedure. First, particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), particulate matter with aerodynamic diameter of less than 2·5 μm ($PM_{2·5}$), blackness of the $PM_{2·5}$ exposed filter ($PM_{2·5absorbance}$), determined by measurement of light reflectance (a marker for soot and black carbon), nitrogen oxides (NOx), and nitrogen dioxide (NO_2) were measured during different seasons at locations for each cohort population between October, 2008, and April, 2011.[18,19] PM_{coarse} was calculated as the difference between PM_{10} and $PM_{2·5}$ (ie, PM with diameter 2·5–10 μm). In three areas, only NO_2 and NOx were measured (figure 1). Second, land-use

regression models were developed for each pollutant in each study area, with the yearly mean concentration as the dependent variable and an extensive list of geographical attributes as possible predictors.[20,21] Generally, predictors for PM_{10}, $PM_{2·5}$, NOx, and NO_2 were related to traffic or roads and population or building density. Variables related to industry, proximity to a port, and altitude were also predictors in some models. The models generally explained a large fraction of measured spatial variation, the R^2 from leave-one-out cross-validation usually falling between 0·60 and 0·80 (appendix p 20). Finally, the models were used to assess

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	Total participants	Age at baseline (years)	All lung cancer	Adeno-carcinoma*	Squamous-cell carcinoma*	PM_{10} (μg/m³)	PM_{coarse} (μg/m³)	$PM_{2·5}$ (μg/m³)	$PM_{2·5absorbance}$ (10^{-5}/m)	NO_2 (μg/m³)	NOx (μg/m³)	Traffic on nearest street (vehicles per day)	Traffic load on major streets within 100 m (vehicle-km per day)
EPIC-Umeå, Sweden	22 136	46·0 (12·2)	69 (0·31%)	34 (0·15%)	18 (0·08%)	NA	NA	NA	NA	5·2 (2·5)	8·7 (5·7)	845 (1530)	102 (417)
HUBRO, Oslo, Norway	17 640	47·8 (15·0)	75 (0·43%)	25 (0·14%)	··	13·5 (3·1)	4·0 (2·0)	8·9 (1·3)	1·2 (0·3)	20·9 (8·0)	38·3 (15·5)	2502 (5117)	821 (1840)
SNAC-K, Stockholm, Sweden	2384	73·1 (10·7)	18 (0·76%)	13† (0·55%)	··	16·4 (6·0)	8·6 (4·8)	8·0 (1·3)	0·8 (0·2)	17·5 (4·9)	33·5 (12·6)	3888 (9886)	2298 (3699)
SALT, Stockholm, Sweden	4732	57·9 (10·2)	29 (0·61%)	12 (0·25%)	··	14·9 (3·9)	7·3 (3·0)	7·3 (1·3)	0·6 (0·2)	10·9 (4·2)	18·9 (9·4)	1460 (3351)	587 (1623)
Sixty, Stockholm, Sweden	3813	60·4 (0·1)	38 (1·00%)	22 (0·58%)	5 (0·13%)	15·0 (3·8)	7·3 (2·9)	7·3 (1·3)	0·6 (0·2)	10·7 (4·2)	18·6 (9·4)	1453 (3466)	512 (1446)
SDPP, Stockholm, Sweden	7116	47·1 (5·0)	35 (0·49%)	22 (0·31%)	5 (0·07)	13·6 (3·2)	6·3 (2·4)	6·6 (1·2)	0·5 (0·1)	8·4 (1·7)	14·4 (3·3)	861 (1621)	110 (423)
DCH, Copenhagen, Denmark	37 447	56·8 (4·4)	638 (1·70%)	236 (0·63%)	106 (0·28%)	17·1 (1·9)	5·7 (1·0)	11·3 (0·9)	1·2 (0·2)	16·3 (7·0)	26·7 (18·4)	2991 (7209)	1221 (2332)
EPIC-MORGEN, Netherlands	15 993	43·7 (10·7)	92 (0·58%)	32 (0·20%)	24 (0·15%)	25·6 (1·7)	8·6 (1·1)	16·9 (0·6)	1·4 (0·2)	23·8 (7·0)	36·5 (11·8)	1535 (4084)	917 (1979)
EPIC-PROSPECT, Netherlands	14 630	57·6 (6·0)	112 (0·77%)	43 (0·29%)	16 (0·11%)	25·3 (1·2)	8·5 (0·7)	16·8 (0·5)	1·4 (0·2)	26·7 (4·6)	39·6 (10·5)	1020 (3433)	678 (1513)
EPIC-Oxford, UK	36 832	45·3 (13·6)	78 (0·21%)	19 (0·05%)	9 (0·02%)	16·1 (2·0)	6·4 (0·9)	9·8 (1·1)	1·1 (0·3)	24·5 (8·0)	40·9 (15·6)	1381 (4345)	373 (1287)
VHM&PP, Vorarlberg, Austria	108 018	42·8 (14·9)	678 (0·63%)	223 (0·21%)	157 (0·15%)	20·7 (2·4)	6·7 (0·9)	13·6 (1·2)	1·7 (0·2)	19·9 (5·5)	40·0 (9·5)	1687 (3582)	294 (991)
EPIC-Varese, Italy	9506	51·6 (8·2)	43 (0·45%)	17 (0·18%)	12 (0·13%)	NA	NA	NA	NA	43·8 (17·3)	86·8 (41·9)	NA	NA
EPIC-Turin, Italy	7216	50·4 (7·6)	48 (0·67%)	23 (0·32%)	··	46·6 (4·6)	16·6 (3·0)	30·1 (2·0)	3·1 (0·4)	53·0 (10·9)	96·2 (21·5)	3903 (9164)	465 (912)
SIDRIA-Turin, Italy	4816	44·0 (6·2)	19 (0·39%)	··	··	48·1 (4·1)	17·0 (2·5)	31·0 (1·7)	3·2 (0·4)	59·8 (10·6)	107·3 (24·3)	4291 (10 202)	810 (1379)
SIDRIA-Rome, Italy	9105	44·3 (6·0)	53 (0·58%)	··	··	36·5 (5·0)	16·7 (3·4)	19·4 (1·8)	2·7 (0·5)	39·1 (9·1)	82·0 (23·9)	2956 (6728)	1392 (2825)
EPIC-San Sebastian, Spain	7464	49·4 (7·7)	52 (0·70%)	··	··	NA	NA	NA	NA	23·8 (6·6)	47·1 (12·5)	NA	673 (2614)
EPIC-Athens, Greece	4096	49·0 (11·7)	18 (0·44%)	6 (0·15%)	··	45·2 (13·7)	20·8 (2·6)	20·4 (2·7)	2·3 (0·5)	38·0 (13·7)	75·5 (41·0)	9073 (12 512)	11 000 (15 000)

Data are n, mean (SD), and n (%). PM_{10}=particulate matter with diameter <10 μm. PM_{coarse}=particulate matter with diameter 2·5–10 μm. $PM_{2·5}$=particulate matter with diameter <2·5 μm. $PM_{2·5absorbance}$=soot. NO_2=nitrogen dioxide. NOx=nitrogen oxides (the sum of nitric oxide and nitrogen dioxide). EPIC=European Prospective Investigation into Cancer and Nutrition. NA=not available. HUBRO=Oslo Health Study. SNAC-K=Swedish National Study on Aging and Care in Kungsholmen. SALT=Screening Across the Lifespan Twin study and TwinGene. Sixty=Stockholm 60 years old and IMPROVE. SDPP=Stockholm Diabetes Prevention Program. DCH=Diet, Cancer and Health study. MORGEN=Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands. VHM&PP=Vorarlberg Health Monitoring and Prevention Programme. SIDRIA=Italian Studies of Respiratory Disorders in Childhood and Environment. ··=No data or too few cases for the model to converge. *Of the lung. †Contributed to results for adenocarcinomas of the lung in participants who lived at the same residence during the whole follow-up, but did not contribute to the results for all participants because the model did not converge.

Table 1: Participants, lung cancer cases, mean air pollution concentrations, and traffic in each cohort

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exposure at the baseline address of each cohort member. We also collected information on two indicators of traffic at the residence: traffic intensity (vehicles per day) on the nearest street and total traffic load (vehicle-km driven per day) on all major roads within 100 m.

Statistical analyses

Proportional hazards Cox regression models were fitted for each cohort, with age as the underlying timescale. Participants were followed up for lung cancer from enrolment until the time of a lung cancer diagnosis or censoring. Participants with a cancer (except non-melanoma skin cancer) before enrolment were excluded. Censoring was done at the time of death, a diagnosis of

any other cancer (except non-melanoma skin cancer), emigration, disappearance, loss to follow-up for other reasons, or end of follow-up, whichever came first. For the analyses of histological subtypes of lung cancer, cases of different histological subtypes were censored.

Air pollution exposure was analysed as a linear variable in three a-priori specified confounder models. Model 1 included sex, calendar time (year of enrolment; linear), and age (time axis). Model 2 additionally adjusted for smoking status (never, former, or current), smoking intensity, square of smoking intensity, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, level of education, and employment status (all referring to baseline). We entered a squared term of smoking intensity because we expected a non-linear association with lung cancer. Model 3 (the main model) further adjusted for area-level socioeconomic status. A cohort was included only if information about age, sex, calendar time, smoking status, smoking intensity, and smoking duration were available.

We assessed individual characteristics as a-priori potential effect modifiers: age (<65 years or ≥65 years), sex, level of education, smoking status, fruit intake (<150 g, 150–300 g, or ≥300 g per day). Age was analysed time dependently. For a few cohorts (HUBRO, Sixty, SDPP) for which there was information about fruit intake in categories such as "a few times per week", "daily", and "several times per day", the lowest category was analysed as less than 150 g per day, the medium category as 150–300 g per day, and the highest category as 300 g per day or greater.

We undertook several sensitivity analyses and model checks for each cohort, all with confounder model 3. First, we restricted the analyses to participants who had lived at the baseline address throughout follow-up to minimise misclassification of long-term exposure relevant to the development of lung cancer. Second, we added an indicator of extent of urbanisation to model 3. Third, we tested the linear assumption in the relation between each air pollutant and lung cancer by replacing the linear term with a natural cubic spline with three equally spaced inner knots, and compared the model fit of the linear and the spline models by the likelihood-ratio test. Fourth, to investigate if an association between air pollution and risk for lung cancer was detectable below a-priori defined thresholds, we ran models including only participants exposed to air pollution concentrations below those thresholds.

In the meta-analysis, we used random-effects models to pool the results for cohorts.[22] I^2 statistics[23] and p values for the χ^2 test from Cochran's Q were calculated to investigate the heterogeneity among cohort-specific effect estimates. Effect modification was tested by meta-analysing the pooled estimates from the different strata with the χ^2 test of heterogeneity. We assessed the
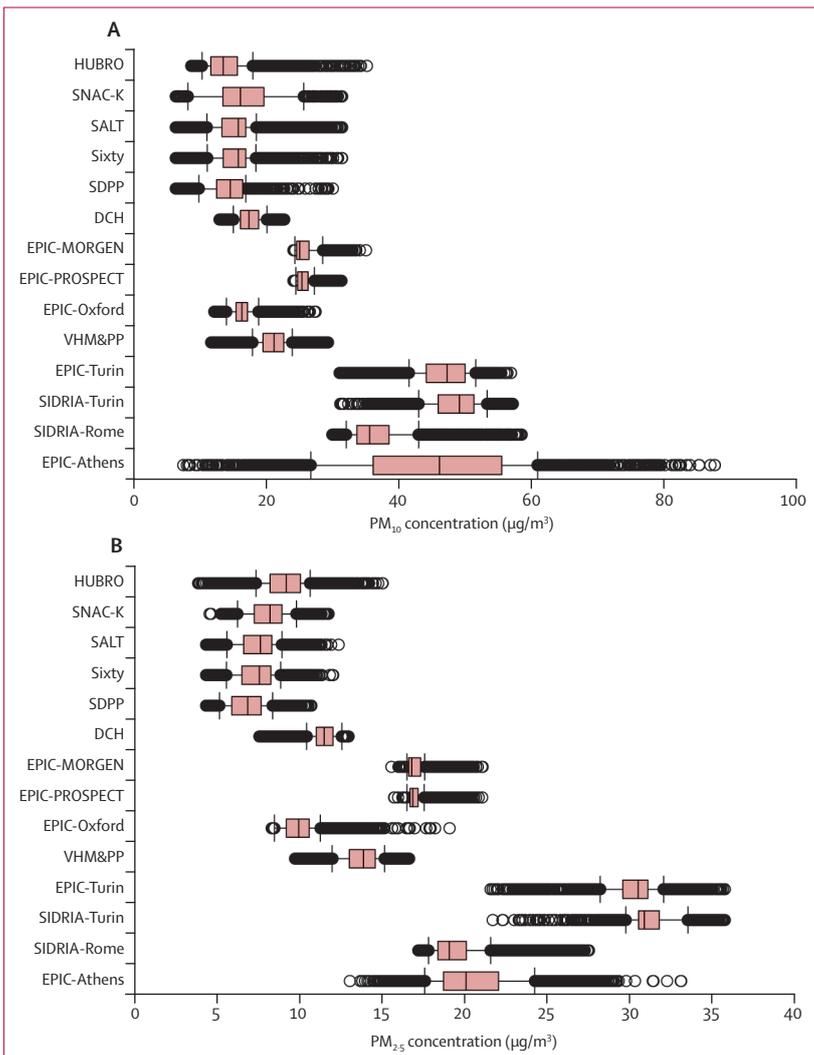
Figure 2: Distribution of particulate matter air pollution at participant addresses in each cohort
PM$_{10}$ concentration (A) and PM$_{2.5}$ concentration (B) in each of the cohort studies. Pink boxes show median (central vertical line) and 25th and 75th percentiles (ends of box); lines extending from the left of each box show the concentration range from the 10th to the 25th percentile; lines extending from the right of each box show the concentration range from the 75th to the 90th percentile. The black circles show each concentration below the 10th percentile and above the 90th percentile. PM$_{10}$=particulate matter with diameter <10 μm. PM$_{2.5}$=particulate matter with diameter <2·5 μm.

robustness of the results by repeating the meta-analysis after exclusion of the two largest cohorts. The proportional hazards assumption of the Cox model was not violated (appendix, p 19).

We used a common STATA script for all analyses, except for spline models, which were fitted with R software. The versions of software used to analyse individual cohorts are listed in the appendix (pp 2–18).

Role of the funding source

The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Authors with access to the raw data included JS and AO (EPIC-Umeå), BO (HUBRO), JP (SNAC-K, SALT, Sixty, and SDPP), ZJA (DCH), RB (EPIC-MORGEN and EPIC-PROSPECT), WWX (EPIC-Oxford and EPIC-Varese), GW (VHM&PP), FR (EPIC-Turin), CG and EM (SIDRIA-Turin), GC (SIDRIA-Rome), IT (EPIC-San Sebastian), and KK (EPIC-Athens). The corresponding author had full access to all analysis results from each cohort and final responsibility for the decision to submit for publication.

Results

The 17 cohorts in nine European countries that contributed to this study contained 312 944 cohort members and contributed 4 013 131 person-years at risk and 2095 incident lung cancer cases that developed during follow-up (average follow-up was 12·8 years). More details of each cohort, including characteristics of the participants, available variables, and their distribution are provided in the appendix (pp 2–18). Most of the cohort studies recruited participants in the 1990s (appendix, pp 2–18). The number of participants and the number of those who developed cancer varied substantially between cohorts, with the Danish (DCH) and Austrian (VHM&PP) cohorts contributing more than half the lung cancer cases (table 1). The cohort areas represented a wide range of air pollution concentrations, with three to 12 times higher mean air pollution levels in some southern European areas than in some northern European areas (table 1). The variation in exposure within study areas was substantial (figure 2; appendix pp 26–28). The mean age at enrolment in each cohort ranged from 43 to 73 years (table 1).

The meta-analysis showed an association with risk for lung cancer that was statistically significant for PM_{10} concentration (hazard ratio [HR] 1·22 [95% CI 1·03–1·45] per 10 μg/m³) in confounder model 3. For $PM_{2.5}$ concentration, the HR was 1·18 (0·96–1·46) per 5 μg/m³, and for traffic load at major roads within 100 m the HR was 1·09 (0·99–1·21) per 4000 vehicle-km per day in confounder model 3 (table 2). The results from model 1, with adjustment only for age, sex, and calendar time, showed stronger associations; the effect of adjustment was due mainly to the smoking variables. Results of models 2 and 3 showed no association between risk for lung cancer and NO_2, NOx, or traffic intensity at the nearest street (table 2). Restriction to the 14 cohorts for whom estimates of exposure to particulate matter were available gave similar results for NO_2 (HR 1·01, 95% CI 0·94–1·09) and NOx (HR 1·03, 0·97–1·10). Figure 3 shows the HRs for each cohort from the meta-analyses for PM_{10} and $PM_{2.5}$. Although the HRs varied substantially across cohorts, the 95% CIs for each cohort always included the overall meta-analysis estimate, and we did not identify any significant heterogeneity between cohorts. The meta-analysis HRs

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See **Online** for appendix

	Increase	Number of cohorts	HR (95% CI)			Measures of heterogeneity between cohorts (model 3)	
			Model 1*	Model 2†	Model 3‡	I^2	p value
PM_{10}	10 μg/m³	14	1·32 (1·12–1·55)	1·21 (1·03–1·43)	1·22 (1·03–1·45)	0·0%	0·83
$PM_{2.5}$	5 μg/m³	14	1·34 (1·09–1·65)	1·17 (0·95–1·45)	1·18 (0·96–1·46)	0·0%	0·92
PM_{coarse}	5 μg/m³	14	1·19 (0·99–1·42)	1·08 (0·89–1·31)	1·09 (0·88–1·33)	33·8%	0·11
$PM_{2.5absorbance}$	10^{-5}/m	14	1·25 (1·05–1·50)	1·09 (0·87–1·37)	1·12 (0·88–1·42)	19·0%	0·25
NO_2	10 μg/m³	17	1·07 (1·00–1·14)	0·99 (0·93–1·06)	0·99 (0·93–1·06)	0·0%	0·70
NOx	20 μg/m³	17	1·08 (1·02–1·14)	1·01 (0·95–1·06)	1·01 (0·95–1·07)	0·0%	0·62
Traffic density on nearest road	5000 vehicles per day	15	1·02 (0·98–1·06)	1·00 (0·97–1·04)	1·00 (0·97–1·04)	0·0%	0·90
Traffic load on major roads within 100 m	4000 vehicle-km per day	16	1·10 (1·00–1·21)	1·07 (0·97–1·18)	1·09 (0·99–1·21)	0·0%	0·92

We included only participants without missing data in any of the variables included in model 3, so the datasets were identical for analyses with all three models. See appendix (p 25) for numbers of participants and lung cancer cases contributing to each meta-analysis result. HR=hazard ratio. PM_{10}=particulate matter with diameter <10 μm. $PM_{2.5}$=particulate matter with diameter <2·5 μm. PM_{coarse}=particulate matter with diameter 2·5–10 μm. $PM_{2.5absorbance}$=soot. NO_2=nitrogen dioxide. NOx=nitrogen oxides (the sum of nitric oxide and nitrogen dioxide). *Model 1: age (timescale in Cox model), sex, calendar time. †Model 2: model 1 + smoking status, smoking intensity, square of smoking intensity, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, education level, and employment status. ‡Model 3: model 2 + area-level socioeconomic status.

Table 2: Meta-analyses of associations between air pollutants and traffic indicators and the risk for lung cancer
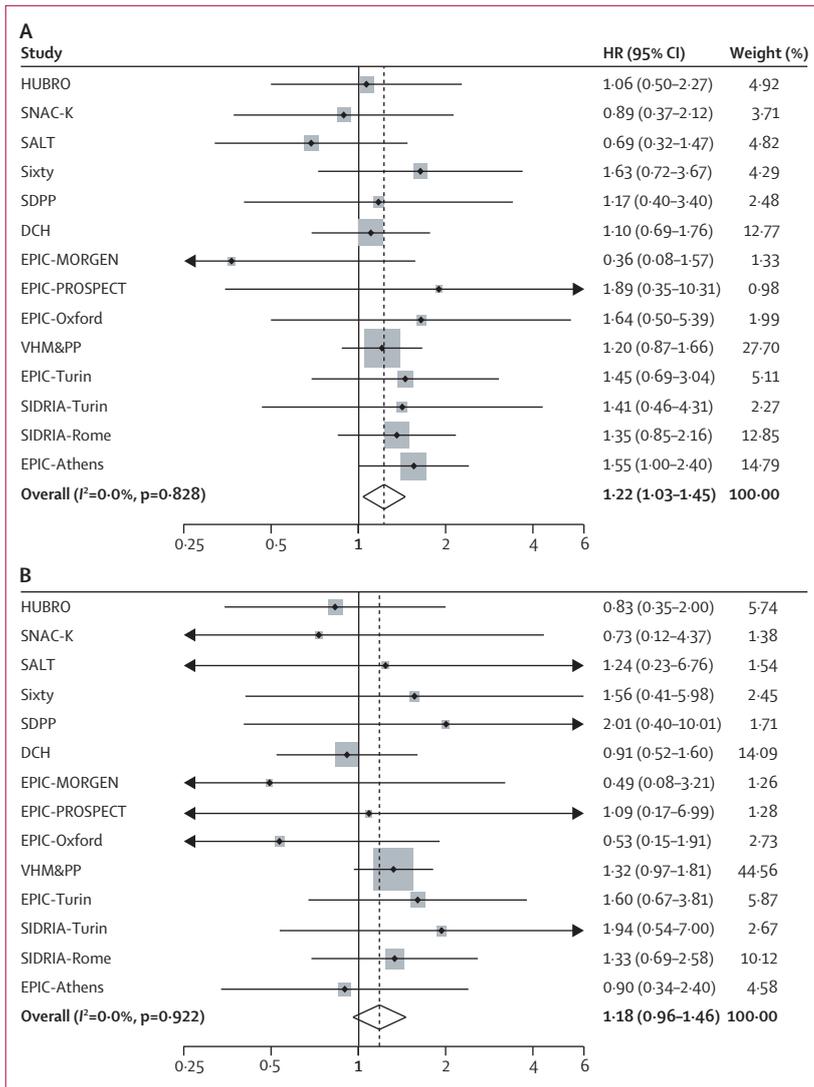
Figure 3: Risk for lung cancer according to concentration of particulate matter in each cohort study
HRs for lung cancer according to PM$_{10}$ concentration (A) and PM$_{2.5}$ concentration (B) in each of the cohort studies, based on confounder model 3. Weights are from random effects analysis. Datapoints show HR; lines show 95% CI; boxes show the weight with which each cohort contributed to the overall HR; vertical dashed line shows overall HR. HR=hazard ratio. PM$_{10}$=particulate matter with diameter <10 μm. PM$_{2.5}$=particulate matter with diameter <2.5 μm.

for PM$_{10}$ and PM$_{2.5}$ were not affected by adjustment for NO$_2$, and the meta-analysis for PM$_{2.5}$ was not affected by adjustment for PM$_{coarse}$ (data not shown). Plots for the other air pollutants and the traffic indicators are presented in the appendix (pp 29–31). Table 3 shows statistically significant associations between PM$_{10}$ and PM$_{2.5}$ and adenocarcinomas of the lung. Restriction to participants who had lived at the same residence throughout follow-up gave consistently stronger associations for all lung cancers combined, and for adenocarcinomas alone (table 3). The stronger associations with adenocarcinomas and for people who had not moved house were not due to selection of cohorts contributing to these results (table 3).

Squamous-cell carcinomas were not significantly associated with particulate matter air pollution.

Restriction of participants to those exposed to air pollution below several predefined thresholds for particulate matter concentrations (including below European Union air quality limit values for PM$_{10}$ [40 μg/m³] and PM$_{2.5}$ [25 μg/m³]) provided consistently raised HRs, although the 95% CIs crossed unity (table 4). This finding is complemented by the results of the spline models (appendix p 22), showing that the association between air pollution and risk for lung cancer did not deviate significantly from linear.

We noted no clear differences between the HRs for lung cancer associated with PM$_{10}$ and PM$_{2.5}$ according to sex, age, level of education, smoking status, or fruit intake (appendix p 23), with widely overlapping CIs for the effect modifier levels; all the p values for interaction were 0·19 or higher. We also noted raised HRs for lung cancer in association with PM$_{10}$ and PM$_{2.5}$ in never-smokers (appendix p 23).

The HRs for lung cancer in association with PM$_{10}$ and PM$_{2.5}$ were virtually identical before and after exclusion of the two largest cohorts (which contributed most of the lung cancer cases; appendix p 24). Adjustment for extent of urbanisation, which could be done in seven cohorts, led to a small change in the HR for PM$_{10}$, which was, however, due almost entirely to selection of contributing cohorts and not to adjustment for urbanisation per se (appendix p 24).

With decreasing air pollution concentrations and contrasts over time, risk estimates based on recent contrast might be too high. We investigated this by back-extrapolating contrast in two cohorts with long-term PM$_{2.5}$ monitoring, and in seven cohorts with long-term PM$_{10}$ monitoring. Results were identical for PM$_{2.5}$ and only slightly lower for PM$_{10}$ when using the back-extrapolated contrasts (appendix p 19).

Discussion

This analysis of 17 European cohort studies shows associations between residential exposure to particulate matter air pollution at enrolment and the risk for lung cancer. The associations were stronger for adeno-carcinomas of the lung and in participants who lived at their enrolment address throughout follow-up.

The strengths of our study include the use of 17 cohort studies in several locations in Europe with very different air pollution exposure levels and also the use of standardised protocols for exposure assessment and data analysis. A comprehensive set of pollutants was assessed, by contrast with many previous studies; few European studies have assessed particulate matter air pollution (panel). Individual exposure assessment was based on actual measurements made in the development of land-use regression models for the detection of within-area contrasts. The study benefits from standardised exposure assessment, a large number of participants,

	Number of cohorts	HR (95% CI) for histological cancer subtype analysis		HR (95% CI) for standard analysis*	
		PM$_{10}$	PM$_{2.5}$	PM$_{10}$	PM$_{2.5}$
All participants					
All lung cancers	14†	1·22 (1·03–1·45)	1·18 (0·96–1·46)	1·22 (1·03–1·45)	1·18 (0·96–1·46)
Adenocarcinomas	11‡	1·51 (1·10–2·08)	1·55 (1·05–2·29)	1·22 (1·01–1·47)	1·16 (0·92–1·45)
Squamous-cell carcinomas	7§	0·84 (0·50–1·40)	1·46 (0·43–4·90)	1·19 (0·94–1·51)	1·18 (0·91–1·52)
Participants who did not change residence					
All lung cancers	10¶	1·48 (1·16–1·88)	1·33 (0·98–1·80)	1·22 (1·02–1·46)	1·20 (0·96–1·51)
Adenocarcinomas	8‖	2·27 (1·32–3·91)	1·65 (0·93–2·95)	1·19 (0·98–1·45)	1·17 (0·92–1·49)
Squamous-cell carcinomas	3**	0·64 (0·28–1·48)	0·65 (0·16–2·57)	1·21 (0·94–1·55)	1·22 (0·93–1·60)

Meta-analysis results based on confounder model 3. See appendix (p 25) for numbers of participants and lung cancer cases contributing to each meta-analysis result. HRs are per 10 μg/m³ of PM$_{10}$ and per 5 μg/m³ of PM$_{2.5}$. HR=hazard ratio. PM$_{10}$=particulate matter with diameter <10 μm. PM$_{2.5}$=particulate matter with diameter <2·5 μm. *Standard analysis, disregarding histological cancer subtype (ie, with all lung cancers as the endpoint and including all participants in the same cohorts as used in the histological cancer subtype analysis). †HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‡HUBRO, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, EPIC-Athens. §Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP. ¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‖HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, VHM&PP, EPIC-Athens. **Sixty, DCH, VHM&PP.

Table 3: Associations between PM$_{10}$ and PM$_{2.5}$ and risk for lung cancer for all participants and those who did not change residence during follow-up, according to histological cancer subtype

information about potential confounders, and a virtually complete follow-up. Only one cohort (EPIC-Athens) used active follow-up with a loss of follow-up information for 335 (6·5%) of the participants; the other cohorts reported complete follow-up by use of registries and administrative systems. The loss of follow-up in the Athens cohort is slight and we see no reason why it should be related to concentrations of air pollution, which could imply risk for bias.

Most results from previous cohort studies of ambient particulate matter air pollution and lung cancer incidence or mortality in general populations showed associations that were statistically significant or of borderline significance,[2,5–9,11,26,27] whereas two studies reported no such association.[13,28] The present study, one of the largest of its kind with 2095 lung cancer cases, estimated an HR of 1·40 (95% CI 0·92–2·13) per 10 μg/m³ of PM$_{2.5}$ (equivalent to HR 1·18, 0·96–1·46 per 5 μg/m³), which is similar to the Harvard Six Cities study[8] estimate in a US cohort (351 cases) of 1·37 (1·07–1·75) per 10 μg/m³ and that from a Canadian study (HR 1·29, 0·95–1·76; 2390 cases),[29] but higher than the estimate from an American Cancer Society study (HR 1·14 1·04–1·23),[2] and from studies in the Netherlands (HR 0·81, 0·63–1·04; 1940 cases),[13] Japan (HR 1·24, 1·12–1·37; 518 cases),[5] China (HR 1·03, 1·00–1·07; 624 cases),[6] and Italy (HR 1·05, 1·01–1·10; 12 208 cases).[11] The CIs of these estimates, however, overlap with ours, so the differences could be due to random variation. Previously estimated associations with PM$_{10}$ differ more widely than those with PM$_{2.5}$. Our estimated HR of 1·22 per 10 μg/m³ of PM$_{10}$ (1·03–1·45) is in line with that of a recent study in New Zealand (HR 1·15, 1·04–1·26; 1686 cases),[7] higher than that in a previous European study (HR 0·91, 0·70–1·18;

	Number of cohorts	HR (95% CI) for threshold analyses	HR (95% CI) for standard analyses†
PM$_{10}$			
15 μg/m³	5‡	1·34 (0·51–3·52)	1·21 (0·87–1·68)
20 μg/m³	8§	1·31 (0·94–1·82)	1·13 (0·92–1·40)
25 μg/m³	10¶	1·17 (0·93–1·47)	1·12 (0·91–1·38)
30 μg/m³	10¶	1·13 (0·92–1·40)	1·12 (0·91–1·38)
35 μg/m³	11‖	1·11 (0·90–1·37)	1·15 (0·95–1·39)
40 μg/m³	12**	1·13 (0·92–1·39)	1·17 (0·97–1·41)
No threshold	14 (all)††	1·22 (1·03–1·45)	1·22 (1·03–1·45)
PM$_{2.5}$			
10 μg/m³	6‡‡	1·20 (0·55–2·66)	0·97 (0·63–1·49)
15 μg/m³	8§§	1·11 (0·85–1·45)	1·15 (0·90–1·47)
20 μg/m³	11¶¶	1·14 (0·90–1·45)	1·16 (0·92–1·45)
25 μg/m³	11¶¶	1·13 (0·90–1·43)	1·16 (0·92–1·45)
No threshold	14 (all)††	1·18 (0·96–1·46)	1·18 (0·96–1·46)

Meta-analysis results based on confounder model 3. See appendix (p 25) for numbers of participants and lung cancer cases contributing to each meta-analysis result. HRs are per 10 μg/m³ of PM$_{10}$ and per 5 μg/m³ of PM$_{2.5}$. HR=hazard ratio. PM$_{10}$=particulate matter with diameter <10 μm. PM$_{2.5}$=particulate matter with diameter <2·5 μm. *Participants living at addresses (at baseline) with air pollution above these thresholds were excluded from the analysis. †Standard analysis, disregarding thresholds (ie, including all participants in the same cohorts as used in the threshold analysis). ‡HUBRO, Sixty, SDPP, DCH, EPIC-Oxford. §HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford, VHM&PP. ¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford, VHM&PP. ‖HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, SIDRIA-Rome. **HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Rome. ††HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, EPIC-Turin, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens. ‡‡SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford. §§HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-Oxford, VHM&PP. ¶¶HUBRO, SNAC-K, SALT, Sixty, SDPP, DCH, EPIC-MORGEN, EPIC-PROSPECT, EPIC-Oxford, VHM&PP, SIDRIA-Rome.

Table 4: Associations between PM$_{10}$ and PM$_{2.5}$ and risk for lung cancer, according to air pollution thresholds*

271 cases),[28] and lower than those in studies in the USA (HR 5·21, 1·94–13·99; 36 cases) per 24 μg/m³ PM$_{10}$,[26] and Germany (HR 1·84, 1·23–2·74; 41 cases) per 7 μg/m³ PM$_{10}$.[9] In most of the previous studies, exposure was monitored at a central site; few estimated exposure at individual addresses, as was done in our study.

Panel: Research in context

Systematic review

We reviewed the scientific literature up to May, 2007, when our grant proposal was submitted to the European Union. We searched the PubMed and Embase databases for articles and reviews published in English with the search terms "air pollution and lung cancer" and "ambient air and lung cancer". A brief description of the findings of our scientific literature review was part of the study proposal. Two published reviews from the period immediately before 2007 were used as a basis of our scientific literature review.[24,25] At the time of the inception of our study, some studies had already provided evidence for an association between air pollution and lung cancer risk, but they had limitations: small size of some of the cohort studies; poor retrospective exposure assessment; absence of or limited information about potential confounders; and mortality used instead of lung cancer incidence as outcome.

Interpretation

Our study supports the role of ambient particulate matter air pollution in the development of lung cancer even at concentrations below current European Union limit values. Our study overcomes several limitations of previous studies, having a large sample size, broad European coverage, retrospective exposure assessment, adjustment for a wide range of potential confounders, and incident lung cancer as the outcome. Particulate matter air pollution is ubiquitous, and on the basis of our results, further reductions in particulate matter air pollution can be expected to reduce the number of lung cancer cases in Europe.

Of the four major histological subtypes of lung cancer, adenocarcinoma is the only one that also develops in a substantial number of non-smokers,[30] so this subgroup is useful to assess for causes other than smoking, compared with, for example, patients with squamous-cell carcinomas. Such causes might include two groups of carcinogenic air pollutants: polycyclic aromatic hydrocarbons and N-nitroso compounds such as nitrosamines. Dissemination of low-tar filter cigarettes has been hypothesised as a cause of the relative increases in incidence rates of adenocarcinomas and decrease in squamous-cell carcinomas of the lung in the USA because the smoke has a lower content of polycyclic aromatic hydrocarbons, which are thought to be associated with squamous-cell carcinoma, and a higher content of nitrates and toxic agents formed from NOx such as nitrosamines, which are associated with adeno-carcinomas.[15,16] Studies of time trends and geographical correlations have suggested that ambient air pollution might also have affected the incidence of adeno-carcinomas,[16,17] whereas one study suggested an association between air pollution and squamous-cell carcinomas of the lung.[14] The present study showed

associations between air pollution and adenocarcinomas of the lung, but not squamous-cell carcinomas. This result suggests that air pollution with nitrates and toxic agents formed from NOx such as nitrosamines might be more important for risk for lung cancer than polycyclic aromatic hydrocarbons in the air. The concentration of polycyclic aromatic hydrocarbons in the air has decreased substantially in many cities in developed countries throughout the past three to four decades.[31]

Our study has some limitations. The effects of single air pollutants are difficult to disentangle in an epidemiological study because pollutants are part of complex mixtures; however, it seems likely that particulate matter is the most important component for cancer risk. In agreement with this notion, diesel engine exhaust was recently classified as a human carcinogen by the International Agency for Research on Cancer.[32] Ambient air pollution contains several known carcinogens and particulate matter with absorbed polycyclic aromatic hydrocarbons, transition metals, and other substances is capable of causing oxidative stress, inflammation, and direct and indirect genotoxicity.[33,34] Associations with particulate matter rather than with NOx thus seem to be plausible.

We used land-use regression models to estimate exposure at the baseline address; however, even the best exposure models incorporate some degree of misclassification. Any misclassification is expected to be non-differential and consequently not to create artificial associations. The uncertainty of the estimated exposure, however, is expected to affect the precision of the estimated HRs (appendix, pp 19). We used data on air pollution for 2008–11 in the development of our land-use regression models but applied them to addresses of participants at baseline (mainly 10–15 years earlier). Results of recent research in Rome, the Netherlands, and Vancouver showed that the spatial distribution of air pollution is stable over 10-year periods,[35] another study showed high correlations between traffic intensities in 1986 and 1996 on Dutch streets,[36] and finally, spatial models for black smoke in the UK provided reasonable predictions, even going back to the 1960s.[37] In our study, exposure was assessed at the enrolment address; relocation during follow-up might have led to misclassification of the exposure relevant to later development of lung cancer. Our results show stronger associations between air pollution and the risk for lung cancer in people who lived at the same address throughout follow-up. The latency for lung cancer can be several decades;[38] our results suggest that more recent exposure to air pollution is also important in the development of lung cancer.

The cohort-specific analyses consistently identified smoking-related variables as the most important confounders, in accordance with the fact that smoking is the most important risk factor for lung cancer. Information about smoking variables was available for

all the cohorts, and we would expect only weak confounding, if any, from exposure to environmental tobacco smoke and the other variables listed in the appendix (p 21). Radon in the residence is an additional potential confounder, but information about radon was not available for any cohort. Radon is probably inversely associated with air pollution concentrations, because radon concentrations are generally low in apartments, which are common in city areas with higher air pollution concentrations. Thus, if confounding by residential radon occurred, we would expect it to lower the HRs for lung cancer in association with air pollution. Although we adjusted thoroughly for smoking in all cohorts, we cannot rule out potential residual confounding, because data for smoking were obtained at enrolment, and we did not account for changes in smoking habits during follow-up. The association was, however, mainly with adenocarcinoma. If residual confounding had occurred, squamous-cell carcinomas should also have been associated with air pollution.

Data for previous lung disease were not obtained, which is a potential weakness of our study because previous lung disease might be associated with both air pollution concentrations and the risk for lung cancer.

The HRs for lung cancer were similar with and without restriction to participants below most of the predefined threshold values, suggesting that exposure of populations to particulate matter air pollution even at concentrations below the existing European Union air quality limit values for PM_{10} (40 μg/m³) and $PM_{2.5}$ (25 μg/m³) might increase the risk for lung cancer. How widely the overall risk estimates from this meta-analysis can be generalised to all European populations is uncertain, but the absence of significant heterogeneity among the HRs obtained for the single cohorts suggests that the overall estimate can be generalised.

In conclusion, this very large multicentre study shows an association between exposure to particulate matter air pollution and the incidence of lung cancer, in particular adenocarcinoma, in Europe, adding substantially to the weight of the epidemiological evidence.

Contributors

OR-N contributed to design, exposure assessment, and interpretation and drafted the manuscript; ZJA contributed to design, the statistical script, and data analyses; RB and KD contributed to design, exposure assessment, the statistical script, and data analyses; ES and MSt contributed to the statistical script; GW contributed to the statistical script and data analyses; BH contributed to the statistical script; PF, MJN, LM, MK, KTE, TE, ME, KM, MW, KdH, M-YT, AR, and CBad contributed to exposure assessment; BB, KK, and PV contributed to design; WWX contributed to design and data analyses; JS, AO, BO, JP, MSø, AV, FR, EM, and IT contributed to data analyses; BF, PES, PN, UDF, NLP, C-GÖ, LF, GP, ATj, PHP, BB-d-M, TJK, HC, GN, SG, VK, CS, FF, PA, MD, and ATr provided local cohort data; CG and GC contributed to exposure assessment and data analyses; GH contributed to design, exposure assessment, and the statistical script. All authors contributed to critical reading of and comments about the manuscript and interpretation of data, and approved the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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