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Ambient air pollution exposure and risk and progression of interstitial lung abnormalities: the Framingham Heart Study

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Abstract

Background—Ambient air pollution accelerates lung function decline among adults, however, there are limited data about its role in the development and progression of early stages of interstitial lung disease.

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Contributors

MBR, MAM and GMH designed the study with contributions from and the approval of all the other co-authors. GO and GRW obtained the Framingham chest imaging data and GMH designed and managed the process for ascertaining ILA status on each image. MBR performed all statistical analyses with assistance from CZ and WL, who reviewed and verified the code. RWH and GMH contributed as experts on interstitial lung disease. IK developed and validated the PM2.5 model and QD developed and validated the models for EC and ozone, under the supervision of JS. PK, DRG, MAM and JS provided input in the study design and interpretation of the data as part of Harvard's Clean Air Research Center. All authors provided critical input and read and approved the final version of the manuscript.

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Aims—To evaluate associations of long-term exposure to traffic and ambient pollutants with odds of interstitial lung abnormalities (ILA) and progression of ILA on repeated imaging.

Methods—We ascertained ILA on chest CT obtained from 2618 Framingham participants from 2008 to 2011. Among 1846 participants who also completed a cardiac CT from 2002 to 2005, we determined interval ILA progression. We assigned distance from home address to major roadway, and the 5-year average of fine particulate matter (PM_{2.5}), elemental carbon (EC, a traffic-related PM_{2.5} constituent) and ozone using spatio-temporal prediction models. Logistic regression models were adjusted for age, sex, body mass index, smoking status, packyears of smoking, household tobacco exposure, neighbourhood household value, primary occupation, cohort and date.

Results—Among 2618 participants with a chest CT, 176 (6.7%) had ILA, 1361 (52.0%) had no ILA, and the remainder were indeterminate. Among 1846 with a preceding cardiac CT, 118 (6.4%) had ILA with interval progression. In adjusted logistic regression models, an IQR difference in 5-year EC exposure of 0.14 µg/m³ was associated with a 1.27 (95% CI 1.04 to 1.55) times greater odds of ILA, and a 1.33 (95% CI 1.00 to 1.76) times greater odds of ILA progression. PM_{2.5} and O₃ were not associated with ILA or ILA progression.

Conclusions—Exposure to EC may increase risk of progressive ILA, however, associations with other measures of ambient pollution were inconclusive.

INTRODUCTION

Interstitial lung disease is a broad category of chronic lung conditions that can progress to irreversible fibrosis and severe respiratory limitation. Many of the interstitial lung diseases have known environmental risk factors, such as tobacco (idiopathic pulmonary fibrosis and others¹), occupational mineral dusts (coal worker's lung, silicosis and other pneumoconioses) and organic dusts (hypersensitivity pneumonitis). Air pollution has been hypothesised to increase risk of interstitial lung disease by triggering inflammatory responses in the pulmonary interstitium.^{2,3} However, evidence to support its role in the early development of interstitial lung disease is limited.⁴

There is mechanistic and human pathological evidence suggesting that ambient particles and ozone (a component of photochemical smog), may injure the pulmonary interstitium, especially at high levels of exposure. For example, chronic exposure to ozone at very high (10–100× ambient) concentrations causes pulmonary fibrosis in animal models.^{5–8} Radio-labelled inhaled nanoparticles have been found to enter the interstitial spaces of the rat lung, where they may remain for months.⁹ Human autopsy specimens from males living in the relatively polluted region of central valley California in the 1990s suggest that ambient particles accumulate and cause interstitial remodelling at the same regions of the lung that are involved in pneumoconioses.¹⁰ However, the common interstitial lung diseases have a long latency period, and it is unclear if ambient air pollution exposure at contemporary levels contributes to risk of these chronic lung diseases.

Chest imaging allows for the detection of interstitial lung abnormalities (ILA) that are associated with accelerated lung function decline and may precede the development of clinical interstitial lung disease.¹¹ A prior study examined associations between 10 year average pollution exposure and ILA, and found that exposure to nitrogen dioxide (NO₂), a

marker of traffic-related pollution, was associated with odds of ILA, while particulate matter and ozone were not.⁴ To date, no studies have examined pollution exposure and longitudinal measures of ILA progression. To further evaluate if ambient pollution exposure is associated with interstitial changes in the lung, we assessed if long-term (5 years average) exposure to ambient air pollutants at home address, including fine particulate matter (PM_{2.5}), elemental carbon (EC; a constituent of PM_{2.5} that may be especially toxic to the lungs^{12–14} and that, like NO₂, correlates with traffic-related pollution), and ozone (O₃) were associated with odds of ILA and interval progression of ILA between chest images among participants of the Framingham Heart Study.

METHODOLOGY

The study population consists of Framingham Offspring and Third Generation Cohort participants, which have been previously described.¹⁵¹⁶ From 2008 to 2011, 2749 of these participants underwent volumetric CT scans of the whole lung as part of the FHS-MDCT2 (Multidetector CT 2) sub-study. This substudy had the following exclusion criteria: weighing < 350 pounds, age <35 years (men) or <40 years (women), and pregnancy. We included 2618 substudy participants with FHS-MDCT2 ILA assessments who had a valid, geocoded home address and attended the corresponding Framingham Offspring Exam 8 (2005–2008) or Third Generation Exam 2 (2008–2011), during which questionnaire and address information was obtained. For 13 CT substudy participants who did not attend the corresponding FHS exam, the most recent earlier exam was used for questionnaire and address data. To assess for interval change in ILA, we examined data from the subset of these participants (N=1846), who previously completed cardiac CT scans between 2002 and 2005 as part of the FHS-MDCT1 (Multidetector CT1) substudy. The Institutional Review Boards of the Boston University Medical Campus, Massachusetts General Hospital (where all CT scans were obtained), Beth Israel Deaconess Medical Center, and Brigham and Women’s Hospital approved this study. All participants provided written consent.

Ambient air pollution exposure assessment

Proximity to the nearest major roadway—We geocoded participants’ home address using ArcGIS 10(ESRI, Redlands, California, USA) and calculated residential distance to the nearest major (A1, A2 or A3) roadway, defined by the US Census feature classification system as a primary highway with limited-access (A1), a primary road without limited-access (A2), or a secondary or connecting road (A3). Based on previous work showing that particle levels diminish to neighbourhood background levels 100–300 m from major roads,¹⁷¹⁸ we examined associations using categories of distance: <100, 100–<200, 200–<400 and >400 m. For consistency with prior work,¹⁹ we also examined associations with distance to road after excluding those who lived more than 1 km from the nearest major road (N=174 in primary model).

PM_{2.5} exposure—We estimated ambient PM_{2.5} concentrations at each residential address using a spatio-temporal model for the Northeastern USA, as previously described.²⁰ The PM_{2.5} model utilised satellite-based Aerosol Optical Depth data, retrieved using the Multi-Angle Implementation of Atmospheric Correction algorithm at 1×1 km resolution, and

ground-level daily PM_{2.5} mass measurements, land use terms and meteorological covariates to estimate daily PM_{2.5} at 200×200 m resolution. Predictions from this model had an excellent mean out-of-sample R² (0.88) and excellent fit of predictions when compared with withheld measurements (slope=0.99).²⁰

We assigned the 5-year (2004–2008) PM_{2.5} concentration at the address recorded at the time of the most recent Framingham exam visit as a measure of recent, longer-term PM_{2.5} exposure preceding the whole lung CT scan. We selected the same 5-year time period preceding CT scan for all participants to avoid confusing differences in exposure due to home location with difference in exposure due to choice of year. This approach is consistent with our previous work and that of others in the field.^{21,22}

EC exposure—We estimated 5-year (2004–2008) ambient EC at each address using a hybrid neural network EC model developed and validated for the Northeastern USA, as previously described.²³ This model uses continuous estimates of EC from the GEOS-Chem (Goddard Earth Observing System) three-dimensional chemical transport simulations²⁴ and a neural network using daily meteorological variables and land use terms, with calibration at monitoring sites, to make EC predictions at 1×1 km resolution. The total annual R² for EC estimates (obtained by regressing monitored values to calibrated values from this model) ranged from 0.71 to 0.75 in 2004–2008.

O₃ exposure—We assigned 5-year (2004–2008) average O₃ at home address using a spatio-temporal prediction model that was developed for the continental USA, as previously described.²⁵ This model (like the EC model) also uses a hybrid neural network to make daily ground-level O₃ predictions based on the continuous estimates of O₃ from the GEOS-Chem transport simulations and land use terms. In addition, model inputs included satellite-estimates of total column O₃ and vertical profile O₃ (a scaling factor derived from the GEOS-Chem model to estimate the fraction of ground-level O₃ in the total column O₃). To account tropospheric reactions of precursors that produce and deplete O₃, the neural network model included emissions inventory daily United States Environmental Protection Agency (USEPA) Air Quality System measures of sulfur dioxide, nitrogen dioxide, nitrogen oxides (NO_x) and volatile organic compounds. O₃ was estimated at a resolution of 1×1 km. The cross-validated annual R² for 8-hour maximum ozone for this model was 0.76×0.78 in the years 2004–2008.²⁵

Questionnaire and census data

At each exam, data were collected from each participant, including home address, demographics, primary occupation, medication use, smoking history, secondhand tobacco exposure in the home and respiratory symptoms and diagnoses. Neighbourhood-level socioeconomic characteristics for each participant's home address were assigned at the census tract level from US Census 2000 data.

Chest CT acquisition and ILA analysis

Inspiratory volumetric whole lung CT scans for FHS-MDCT2 were obtained in the supine position with no administration of contrast using the 64-detector-row CT scanner

(Discovery, GE Healthcare, Waukesha, WI). The cardiac CT scans for FHS-MDCT1 (Lightspeed, GE) were ECG-gated, inspiratory non-contrast scans covering the lung from approximately the level of the carina to the diaphragm.¹¹ The whole lung FHS-MDCT2 scans were used to ascertain the presence or absence of ILA. The cardiac CT scans were used to ascertain if the extent of any ILA progressed or improved in the interval between scanning.

To classify CT scans by the presence or absence of ILA and ILA progression, CT images were uploaded to a Picture Archiving and Communication System workstation (Virtual Place Raijin, AZE, Tokyo, Japan). As described previously, up to three readers (including radiologists and pulmonologists) who were blind to participant information and prior radiological assessments independently scored each CT scan for the presence or absence of ILA using a sequential reading method.²⁶ The third reader resolved discrepancies. ILA was defined as non-dependent changes, including ground-glass or reticular abnormalities, diffuse centrilobular abnormalities, non-emphysematous cysts, honeycombing or traction bronchiectasis affecting more than 5% of any lung zone. CT scans with focal or unilateral abnormalities were considered indeterminate because unilateral findings are common and often the result of an isolated insult to the lung (eg, prior infection) rather than a diffuse interstitial process.²⁶ After consensus review, participants with a determination of ILA on either the cardiac or subsequent whole lung CT had both sets of images simultaneously compared and scored on a 5-point scale (definite regression, probable regression, no change, probable progression and definite progression). Progression was defined as an increase in lung areas affected with non-dependent ground-glass, reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, honeycombing or traction bronchiectasis, or a new appearance of at least one such abnormality (and regression was defined as a decrease in any of those abnormalities).¹¹ As in prior work,^{11,27} those with ILA and no change or definite/probable regression were categorised as 'ILA without progression' (ie, stable or improved ILA), and those with ILA with probable or definite progression were categorised as 'ILA with progression'. The remaining sets of CT scans were categorised as indeterminate for ILA progression, or as no ILA on either CT.

Statistical methods

We constructed logistic regression models to assess the odds of ILA on volumetric chest CT scan in relation to each measure of pollution exposure. Among the subset of 1846 participants with sequential CT scans, we constructed multinomial logistic regression models to evaluate associations between each exposure and odds of ILA progression compared with the reference category of no ILA progression and no ILA. These models included a category for the 36 participants with stable to improving ILA. All models adjusted for age at CT scan, sex, body mass index, median value of owner-occupied housing in the census block group in 2000, personal educational attainment, smoking status (current, former or never), packyears of smoking (as a continuous variable), any household smoking, cohort and date of CT scan. These covariates were determined a priori and are consistent with our previous publications in this cohort.^{11,19,28,29} Since occupation can be an important source of pollution exposure^{30,31} that can contribute to risk of ILA,³² we also adjusted for primary occupational category (labour, sales/homemaker, professional, or other/unspecified

as defined previously³³) in all models. The category of labour includes skilled labour (eg, plumber, carpenter, painter, hairdresser), general labour (eg, custodian, delivery, mailman, truck driver), and heavy labour (eg, construction, landscaping), and therefore includes participants most likely to have experienced high workplace exposure to particles and fumes. We did not adjust for race/ethnicity because nearly all participants are of European ancestry. We included participants with complete exposure, covariate and outcome data in our models. Only 27 participants in the primary models had missing covariates of adjustment.

For ease of interpretation, results for all associations with 5-year average PM_{2.5}, EC and O₃ were scaled to an IQR difference in exposure (the distance between the 25th percentile and 75th percentile of the exposure distribution in the study population). We evaluated the linearity of each association by fitting 3 degree of freedom splines in generalised additive models (GAM) with a binomial distribution, and compared the fit of these to linear models using likelihood ratio tests. We compared the distribution of pollutant exposure among those with indeterminate CT scans to the other groups, and repeated analyses for odds of ILA and ILA progression using multinomial logistic regression models with a category for indeterminate CT status. We performed sensitivity analyses excluding 675 participants who either did not attend the Framingham exam closest to the CT date (N=13) or who moved between Framingham Offspring Exam 7 (1998–2001) and 8 (2005–2008) or between Third Generation Exam 1 (2002–2005) and 2 (2008–2011), and therefore may not have resided at the same home address location for the full 5-year period from 2004 to 2008. Consistent with our prior work examining respiratory responses to air pollution exposure,¹⁹²⁸²⁹ we performed sensitivity analyses excluding current smokers (N=188) in order to rule out the possibility that acute inflammatory responses to tobacco smoking influenced associations between pollution and ILA, despite adjustment for smoking status and packyears. Also, prior research has found that associations between pollutant exposures and ILA were greater among never smokers than current or former smokers.⁴ Therefore, we tested if associations between each pollutant and ILA differed by smoking status (never, former, current) by adding an interaction term to our models. Finally, we tested for effect modification by sex.

Scaled regression coefficients and ORs were reported with 95% CIs. Analyses were performed in SAS V.9.4 using Proc LOGISTIC, with a glogit link for all multinomial models. All splines were fit using R (R V.3.4.0, R Foundation for Statistical Computing, Vienna, Austria). We used a threshold interaction term p value of <0.05 for statistically significant effect modification and for the likelihood ratio test comparing nested linear and non-linear GAM models.

RESULTS

Study participants

Participant characteristics and outcomes are listed in table 1. Mean participant age was 59.5 years, with an equal representation of each sex. Current smoking was rare (7.2%) but slightly more than half of participants had a history of smoking (51.4%) and a quarter of participants had lived with a smoker during adulthood. The majority attended at least some college and nearly half of participants (46.8%) had a college degree. By census tract, the median value of owner-occupied housing was \$223 000 with a broad distribution. Among

the 2618 participants having undergone full chest CT scans, 6.7% had ILA, 52.0% had no ILA and the remaining scans were indeterminate for ILA. Among the 1846 participants with both cardiac and subsequent chest CT scans, 6.4% had ILA with interval progression, 2.0% had ILA without progression (ie, stable or improved ILA), 35.0% had no ILA on either CT, and the remainder was indeterminate for ILA on at least one CT scan.

Exposure distributions

The median distance to the closest major roadway was 259.8 m. At the time of their Framingham visit, 28.2% of participants lived within 100 m, 14.2% lived between 100 and 200 m and 21.6% lived between 200 and 400 m of a major road. The distribution and correlation of the 5-year pollutant averages are in table 2. The median (IQR) 5-year average $PM_{2.5}$ concentration was 9.9 (1.3) $\mu\text{g}/\text{m}^3$. EC—which is a constituent of $PM_{2.5}$ related to traffic, especially diesel pollution—was moderately correlated with $PM_{2.5}$ (Spearman correlation coefficient of 0.45). O_3 was negatively correlated with EC (Spearman correlation coefficient -0.29) and with $PM_{2.5}$.

Associations with ILA and ILA progression

Associations between air pollution, ILA and ILA progression are summarised in table 3. All results are reported as associations with an IQR difference in the 2004–2008 pollutant exposure, thereby contrasting the odds of ILA and ILA progression at the 75th percentile of pollutant exposure compared with the 25th percentile. An IQR difference in the 2004–2008 average EC level at home address was associated with a 1.27 (95% CI 1.04 to 1.55) times greater odds of ILA, and a 1.33 (95% CI 1.00 to 1.77) times greater odds of ILA with interval progression. We did not observe any statistically significant evidence of departures from linearity for EC or any of the pollutants with ILA (all p values for likelihood ratio test >0.05). There was a pattern of greater odds of ILA and ILA progression among those living within 400 m of a major road, but the CIs crossed the null for all distance categories. There were no convincing associations of 2004–2008 average $PM_{2.5}$ or O_3 with odds of ILA or ILA progression (table 3).

Participants with indeterminate CT scans did not differ from those without ILA or without ILA progression on CT with respect to pollution exposure (online supplementary eTables 1 and 2), and results were similar in multinomial regression models with a category for participants with indeterminate CT scans (online supplementary eTable 3). Associations with distance to road remained inconclusive after excluding those living >1 km from a major road from the reference group. In sensitivity analyses excluding participants who moved (online supplementary eTable 4) and current smokers (online supplementary eTable 5), the associations between EC and ILA progression were unchanged, while associations of EC with ILA were attenuated. There was no statistical evidence that the association between any pollutant and odds of ILA varied by smoking status (joint $P_{\text{interaction}} >0.05$ for all models). There was evidence of effect modification by sex for associations between EC and ILA ($P_{\text{interaction}} = 0.04$). Among men, an IQR increment in 5-year EC exposure was associated with a 1.48 (95% CI 1.15 to 1.91) higher odds of ILA, while the association between EC and ILA was absent among women ($p=0.78$).

DISCUSSION

In this community-dwelling adult population, higher long-term exposure to EC, an indicator of traffic pollution, was associated with greater odds of ILA and progression of ILA on sequential chest imaging. These findings are consistent with the small number of published studies evaluating traffic-related pollution and risk of subclinical or clinical interstitial lung disease,³⁴ and lend some support to the hypothesis that long-term exposure to traffic-related pollution may lead to interstitial remodelling. However, associations with proximity to road were not significant, and there was no association between PM_{2.5} and ILA or ILA progression.

One prior study has evaluated the association between long-term ambient air pollution exposure and measures of early undiagnosed interstitial lung disease.⁴ Among 2671 MESA Lung study participants with ILA determinations, 10-year residence-specific exposure to NO_x estimated by a community-level spatio-temporal model was associated with higher odds of ILA (OR 1.77, 95% CI 1.06 to 2.95 per 40 ppb in NO_x). In the MESA population, the within-centre IQR of 10-year NO_x ranged from 5.2 to 14.2 ppb (data courtesy of Dr Sacks). In MESA, a 13.1 ppb increment in 10-year NO_x (equivalent to the IQR among MESA participants in the New York City area in the Northeastern USA), was associated with a 1.21 (95% CI 1.02 to 1.43) times greater odds of ILA. This is very similar in magnitude to our finding that an IQR increment in 5-year average EC of 0.14 (µg/m³) was associated with a 1.27 (95% CI 1.04 to 1.55) times greater odds of ILA, and a 1.33 (95% CI 1.00 to 1.76) times greater odds of ILA progression.

Recent studies have found that higher short-term (6 week) exposure to O₃ is associated with progression of interstitial lung disease as measured by acute exacerbations of known pulmonary fibrosis.^{34,35} However, we found no evidence that differences in long-term exposure to O₃ was associated with risk of ILA or ILA progression. In fact, associations between O₃ and ILA were in the weakly protective direction, which has been noted in other studies,³⁴ and is possibly a consequence of quenching of O₃ by traffic-related nitric oxide. In our study population, long-term EC and O₃ were negatively correlated, consistent with the known depletion of O₃ in the near-road environment. This quenching of O₃ in areas with high traffic density is also reflected at a national level in our O₃ model: estimated O₃ levels were higher in rural than urban areas across the continental USA.²⁵ Acute and subacute exposure to O₃ appears to be a trigger for respiratory hospitalisation for patients with pulmonary fibrosis^{34,35} and chronic airway disease, such as asthma and COPD.^{36–38} However, we found no convincing evidence that higher long-term O₃ exposure within the ambient levels experienced by our study population (median annual level 38.4 ppb, IQR 1.8 ppb) increases risk of developing interstitial lung disease.

There is some mechanistic evidence to support a causal association between exposure to traffic-related pollution, in particular diesel traffic particles (of which EC is a marker) and interstitial fibrosis. A unifying mechanism is the ability of ultrafine particles and gases in diesel exhaust to induce oxidative stress by producing excess reactive oxygen species, that may activate pro-fibrotic pathways in the pulmonary interstitium.²³⁹ Controlled exposure of diesel exhaust particles has been found to increase expression of mediators of fibrogenesis,

including alteration of nuclear factor-kappa B- and TGF-beta-mediated mechanisms in animal models.^{40,41} Some,⁴² but not all⁴³ studies have suggested that long-term exposure to diesel particles may trigger an epithelial-mesenchymal transition in human bronchial epithelial cells, which is one proposed mechanism for the development of idiopathic pulmonary fibrosis. More mechanistic studies involving controlled, long-term pollutant exposures at contemporary levels are needed to determine if ambient particles or gases can induce interstitial fibrotic changes.

Our study is novel in that we may be the first to examine long-term exposure to major ambient pollutants at home address using validated spatially and temporally resolved pollutant models and longitudinal measures of ILA. ILA progression, defined by worsening ILA on repeated imaging, is more likely to be indicative of a chronic, active interstitial process than a single measure of ILA, as confirmed by previous work by members of our group associating this measure with lung function decline and mortality.¹¹ It is also notable that we examined associations between pollutant exposures and ILA in a region where pollutant levels are relatively low. For example, the mean ambient 5-year PM_{2.5} level was 9.7 (µg/m³) in our study population, which is lower than the mean level of 16.8 µg/m³ in the MESA Lung study,⁴ and well within current air quality standards in the USA and Europe. Additionally, we accounted for a robust list of potential confounders in all our analyses evaluating pollution and ILA, including individual demographic and lifestyle factors, including occupation, and individual-level and neighbourhood-level indicators of socioeconomic position.

Our study has some limitations. We had incomplete longitudinal chest imaging data on 772 participants (out of 2618) who completed the chest CT scan but not the preceding cardiac CT. Therefore, there is potential for bias due to incomplete case analysis for odds of ILA progression. In addition, consistent with prior studies in other populations,²⁷ a large proportion of CT scans were indeterminate for ILA. This is due to the fact that unilateral or focal abnormalities (eg, due to prior infection) are very common and were classified these as indeterminate, because they are not necessarily indicative of a diffuse interstitial pulmonary process. We found that participants with indeterminate CT scans did not differ from those without ILA or without ILA progression on CT with respect to pollution exposure (online supplementary eTables 1 and 2) and there were no associations between exposure to any pollutant and odds of indeterminate ILA or indeterminate ILA progression (all OR very close to 1.0, online supplementary eTable 3). Therefore, excluding those with indeterminate CT imaging in our primary analyses is unlikely to be a major source of bias. Although we have adjusted for a robust list of potential individual-level and neighbourhood-level confounders, we cannot exclude the possibility of residual confounding, for example, by individual-level income (which was not measured in this cohort) or by occupational exposures that may be correlated with neighbourhood-level pollution and were not captured in our categorical variable for primary occupation.

We assigned ambient pollution exposure at home address (where most people spend the majority of their time) as a measure of average exposure. While many Boston-area studies have found that outdoor pollution levels are highly correlated with levels inside the home due to infiltration of outdoor air, especially for PM_{2.5} and elemental or black carbon,^{44,45}

there are differences between these modelled outdoor estimates and the personal exposures of each participant at home and at the workplace. Although we adjusted for primary occupational category, including labour, this is only a crude indicator of lifetime occupational exposure to pollution. These differences further diminish the precision of the pollutant exposure estimates, and reduce our power to detect associations. Proximity to roadway is a singular measure of distance that does not take into account how long the participant lived at a given address, nor does it consider proximity of the home to other roads. While EC is an integrated measure of traffic-related pollution around the home, it is only resolved to 1×1 km and does not capture micro-scale differences in near-roadway pollution exposure. It also does not account for indoor exposures to EC from home-related sources such as wood stoves and fireplaces, which can be important sources of EC exposure in some households, especially during the winter.⁴⁶ Exposure to each pollutant was assigned using spatiotemporal models with different inputs (satellite data for PM_{2.5} and O₃, chemical transport simulation data for O₃ and EC, and land use terms for all models). While the agreement with ground-level measures was good for each of these pollutant models, modelled data provides only an estimate of ground-level exposure. Exposure misclassification due to model error is likely to be non-differential with respect to ILA risk, and therefore should bias our results towards the null and not cause overestimation of associations. Due to the fact that address data were collected only at the time of Framingham Heart Study visits, and the fact that our modelled pollutant exposures only became available around the year 2000 when estimates could be calibrated against EPA ground monitors, we were unable to assess childhood or lifetime exposures to air pollutants. Exposures during childhood or early adulthood may be especially relevant in fibrotic interstitial lung disease because of the long latency period. Future work, including adult cohort studies with longitudinal address and highly resolved exposure data capturing a large proportion of the lifetime, may address these limitations.

In conclusion, in this study, people with a higher long-term exposure to EC, a measure of traffic particle pollution, had higher odds of ILA and progression of ILA over time compared with those with lower EC exposure levels. This may suggest that traffic pollution increases risk of sub-clinical interstitial lung disease, however, associations with other measures of pollution were inconclusive.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

What is the key question?

- Is long-term exposure to air pollution associated with the development and progression of early stages of interstitial lung disease?

What is the bottom line?

- Higher 5-year average exposure to elemental carbon, an indicator of traffic pollution, was associated with greater odds of interstitial lung abnormalities and progression of interstitial lung abnormalities on sequential chest imaging, while associations with other pollutants such as fine particulate matter and ozone were inconclusive.

Why read on?

- This study uses repeated chest imaging and validated spatio-temporal models of daily outdoor air pollution exposure at home address in a large prospective study of generally healthy community-dwelling adults, and the findings lend some support to the hypothesis that long-term exposure to traffic-related pollution may lead to interstitial remodelling.

Table 1

Participant characteristics. data calculated from 2618 participants enrolled in the chest CT substudy with ILA measures

Demographics	Mean (SD) or %
Age (years)	59.5 (11.9)
Male sex (%)	49.6
Body mass index (kg/m ²)	28.5 (5.4)
Smoking status (%)	
Never	48.2
Former	44.2
Current	7.2
Pack-years	9.9 (16.0)
Former smokers	17.1 (17.2)
Current smokers	32.8 (15.2)
Smoker In household In adulthood (%)	25.8
Primary occupation (%)	
Labour	7.6
Sales/Homemaker	25.9
Professional	40.6
Other/Unspecified	25.8
Education (%)	
High school or less	21.6
Some college	31.4
College grade	46.8
Median value of owner-occupied housing in census block group (year 2000 \$)	223 000 (111 000)
ILA on chest CT (among 2618 with chest CT)	
ILA	6.7
No ILA	52.0
Indeterminate	41.3
ILA progression (among 1846 with chest and cardiac CT)	
ILA progression	6.4
Stable/Improved ILA	2.0
No ILA on either CT	35.0
Indeterminate	56.7

ILA, interstitial lung abnormalities.

Table 2

Distributions and correlation of 2004–2008 pollutant exposure averages

	unit	N	Median	IQR width	Range	Spearman correlation coefficient (95% CI)		
						PM _{2.5}	EC	O ₃
PM _{2.5}	µg/m ³	2319	9.9	1.3	2.0–15.9	1		
EC	µg/m ³	2321	0.44	0.14	0.15–1.43	0.45 (0.41 to 0.48)	1	
O ₃	ppb	2584	38.4	1.8	24.4–50.7	-0.16 (-0.20 to -0.12)	-0.29 (-0.32 to -0.25)	1

EC, elemental carbon; PM_{2.5}, 5-year average of fine particulate matter.

Table 3

Associations of exposure to traffic and pollutants with odds of ILA and ILA progression

Exposure	Odds of ILA versus no ILA		Odds of ILA with progression versus no ILA on either CT		Odds of ILA without progression versus no ILA on either CT	
	Model N	OR (95% CI)	Model N	OR (95% CI)	Model N	OR (95% CI)
Proximity to road (vs 400 m)	1497		787			
<100m		1.09 (0.68 to 1.73)		1.30 (0.69 to 2.43)		-
100-<200m		1.21 (0.68 to 2.14)		2.08 (0.98 to 4.44)		-
200-<400m		1.25 (0.76 to 2.06)		1.00 (0.50 to 2.01)		-
PM _{2.5}	1343	1.02 (0.85 to 1.23)	709	1.14 (0.87 to 1.50)		1.45 (0.92 to 2.28)
EC	1344	1.27 (1.04 to 1.55)	709	1.33 (1.00 to 1.77)		1.32 (0.82 to 2.13)
O ₃	1495	0.91 (0.78 to 1.06)	787	0.97 (0.78 to 1.21)		0.92 (0.67 to 1.27)

* All models were adjusted for age, sex, body mass index, smoking status, packyears of smoking, any household smoking during adulthood, median value of owner-occupied housing in the census block group in 2000, education, primary occupation, cohort and date. OR's for ILA without progression by proximity to road category are not shown due to small sample size and wide CIs. OR's for associations with pollutants scaled per IQR in exposure: 1.3 µg/m³ in 2004–2008 PM_{2.5}, 0.14 µg/m³ in 2004–2008 EC, and 1.8 ppb in 2004–2008 O₃.

EC, elemental carbon; ILA, interstitial lung abnormalities; PM_{2.5}, 5-year average of fine particulate matter.