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Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study

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At a Glance Commentary: Scientific Knowledge on the Subject: Short-term exposure to air pollution has been associated with exacerbation of chronic obstructive respiratory disease (COPD) whereas the role of long-term exposures on the development of COPD is not yet fully understood, due in part to the lack of prospective cohort data. What This Study Adds to the Field: We found positive association between first ever hospital admission for COPD and 35 year accumulated exposure to traffic-related air pollution at home address. This study adds to the evidence that air pollution may contribute to the development of COPD, utilizing several novel approaches: use of 35 years accumulated exposure of modelled levels of NO_2; use of objective measure of COPD incidence in terms of the first ever hospital admission for COPD; assessment of the role of co-morbid conditions (asthma and diabetes) in modifying the effect of air pollution on COPD.

This article has an online data supplement, which is accessible from the issue's table of content online at www.atsjournals.org

Abstract

Rationale: Short-term exposure to air pollution has been associated with exacerbation of chronic obstructive respiratory disease (COPD) whereas the role of long-term exposures on the development of COPD is not yet fully understood.

Objectives: We assessed the effect of exposure to traffic-related air pollution over 35 years on the incidence of COPD in a prospective cohort study.

Measurements: We followed 57 053 participants in the Danish Diet, Cancer and Health cohort in the Hospital Discharge Register for their first hospital admission for COPD between 1993 and 2006. We estimated the annual mean levels of nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) at all residential addresses of the cohort participants since 1971 to an event or 2006 and used indicators of traffic near the residential address at recruitment. We assessed the association between exposure to air pollution and COPD incidence by Cox regression analyses for the full cohort, and for participants with and without co-morbid conditions including asthma, diabetes, or cardiovascular disease.

Main results: A first hospital admission for COPD was recorded for 1 786 (3.4%) of 52 799 eligible subjects between recruitment (1993-1997) and 2006. COPD incidence was associated with the 35-year mean NO_2 level (hazard ratio 1.08; 95% confidence interval 1.02-1.14, per interquartile range of 5.8 $\mu g/m^3$), with stronger associations in subjects with diabetes (1.29; 1.05-1.60) and asthma (1.19; 1.03-1.38).

Conclusions: Long-term exposure to traffic related air pollution may contribute to the development of COPD with possibly enhanced susceptibility in people with diabetes and asthma.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory condition of the airways, pulmonary vessels, and lung parenchyma, which is projected to be the third leading cause of death and the fifth leading cause of disability by 2020.[1-3] Cigarette smoking is responsible for the vast majority of COPD, but it does not explain the increasing prevalence worldwide, and occupational and environmental factors are increasingly thought to play important roles.[1] With rapid urbanization of the world population, a better understanding of the harmful effects of exposure to urban air pollution, mainly from traffic, on COPD is important for urban planning, transport legislation, patient management, and prevention. Compelling epidemiological evidence has established that exposure over several days to elevated levels of air pollution exacerbates pre-existing COPD, resulting in increased morbidity and mortality.[4] Solid evidence is, however, lacking for the role of low-level exposure to air pollution in urban environments over years or decades in the development and progression of COPD, due in part to the limited number of prospective cohort studies addressing this problem.[1-3]

The plausible biological mechanism of air pollution damage to the lungs involves a local inflammatory response in the lung tissues with a secondary systemic inflammatory response.[5] Repetition of this inhalation injury is believed to be central to the effects of long-term exposure to air pollution and to the chronic and progressive nature of COPD.[3] This mechanism seems to be well supported by the studies linking COPD to long-term exposure to indoor air pollution from solid fuel (wood smoke) used for cooking and heating in developing countries.[6] However, the epidemiological evidence supporting the notion that chronic exposure to traffic-related air pollution can cause COPD is still limited. Long-term exposure to traffic-related air pollution has been associated with overall and cardiopulmonary mortality[7] and COPD mortality,[8] which was recently confirmed in a study with multi-

pollutant models and improved control for occupational exposures.[9] Several studies have reported link between high levels of air pollution and the prevalence of COPD,[10-12] and none to date studied COPD incidence. Impaired lung function, an important measure of respiratory health and a predictor of COPD mortality and morbidity,[13] has been associated with long-term exposures to air pollution,[11, 13,14] but two recent studies failed to replicate this finding.[15,16] Most previous studies were, however, cross-sectional, with an intrinsic inability to separate the timing of exposure and effect, preventing inferences about causality. Two recent longitudinal cohort studies associated improvements in air pollution levels with attenuated lung function decline[17] and reduced rates of respiratory symptoms,[18] providing more clues about the dynamics behind long-term air pollution exposures and development of chronic respiratory disease.

We studied the effect of exposure to traffic-related air pollution over several decades on the incidence of COPD, defined at first-ever hospital admission for COPD, in a prospective cohort of 57 053 Danish adults with detailed residential address history and information on co-morbidity, including asthma, cardiovascular disease, and diabetes. Exposure to air pollution at each residential address was assessed individually for up to 35 years in a validated dispersion model based on detailed traffic, geographical, and meteorological data, emission factors, and registers covering the whole of Denmark.

Methods

Design and health outcome

We used the cohort of the Danish Diet, Cancer, and Health (DCH) study consisting of 57 053 people aged 50-64 years who lived in Copenhagen or Aarhus between 1993 and 1997.[19] A self-administered questionnaire at baseline (1993-1997) elicited information on smoking and dietary habits, education, occupational history, and lifestyle. Using the unique personal

identification numbers, we linked the cohort to: the Danish Hospital Discharge Register, dating back to 1976, to identify hospital admissions using primary discharge diagnoses for COPD (ICD-10: J40-44) asthma (J45-46), ischaemic heart disease (I20-25), other heart disease (I42-50), stroke (I60-63), and diabetes (E10-14); the Central Population Registry to obtain date of death or emigration and detailed residential address history (1971-2006); and the Danish Address Database to obtain geographical coordinates. The incidence (date of first admission) of COPD between baseline and 27 June 2006 was the main outcome. Co-morbidity (with asthma, ischaemic heart disease, other heart disease, stroke, or diabetes) was defined as at least one hospital admission for the specified diagnosis any time between 1976 and 2006.

Exposure assessment

Exposure was assessed from the residential address history of each cohort member since 1971, which was used to model outdoor levels of nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) with the Danish AirGIS dispersion modeling system,[20] described in detail in an online data supplement. Annual mean NO_2 and NO_x levels were calculated at the available addresses of cohort members with an 80% or more complete residential history (97.6% of the cohort). Missing values, due to missing address or missing geographical coordinates, were substituted by the levels calculated for the preceding address, or when the first address was missing, for the subsequent address. We thus obtained a complete series of annual mean NO_2 and NO_x concentrations at the residential addresses of each cohort member since 1971. We defined three proxies of long-term exposure to air pollution: 35-, 25-, and 15-year time-weighted mean NO_2 and NO_x levels, from 1971, 1981, and 1991, respectively, until the end of follow-up (admission for COPD, death, emigration, or 27 June 2006), to assess the effect of different lengths of exposure on COPD incidence.

We also defined two air pollution proxies based on traffic data at the residential address at recruitment (1993-1997): the presence of a major road (density ≥ 10 000 vehicles/day) within a 50m radius, and traffic load, defined as the total number of kilometers driven by vehicles within a 200m radius.

Statistical methods

We used a Cox proportional hazards model to study association between COPD incidence and exposure to air pollution, with age as the underlying time, left truncation at age at recruitment, and right censoring at age at admission for COPD, death, emigration, or 27 June 2006. The effects of different air pollution proxies were evaluated in separate models, with adjustment for a-priori defined confounders, in three steps: (1) age; (2) also including smoking status, duration, and intensity, and environmental tobacco smoke (ETS); and (3) also including occupational exposure, body mass index (BMI), educational level, and fruit consumption, all defined as shown in Table 1. We also evaluated other confounders including gender, alcohol consumption, physical activity, and vegetable consumption. Levels of NO_2 and NO_x were log-transformed, modeled as time-dependent variables, and the estimates are reported per interquartile range increase. Smoking intensity was calculated by equating a cigarette to 1g, a cheroot or a pipe 3g, and a cigar 5g of tobacco. Occupational exposure was defined as a minimum of 1 year employment in: mining, electroplating, shoe or leather manufacture, welding, painting, steel mill, shipyard, construction (roof, asphalt, or demolition), truck, bus, or taxi driver, asbestos or cement manufacture, asbestos insulation, glass, china, or pottery manufacture, butcher, auto-mechanic, waiter, or cook, and reflects occupation earlier related to chronic lung disease, with focus on lung cancer, as this cohort was designed primarily to study cancer. ETS is an indicator of exposure to second-hand smoke at home or work for minimum 4 hours/day. The potential effect modifiers of an association between a traffic proxy and COPD incidence, in terms of baseline characteristics and co-morbid conditions were

evaluated by introducing interaction terms into the model, and tested by Wald test. The results are presented as hazard ratios (HR) with 95% confidence intervals, estimated with Proc PHREG, SAS 9.2.

Relevant Danish ethical committees and data protection agencies approved the study, and written informed consent was obtained from all participants.

Results

Of the 57 053 cohort members, we excluded 571 with a cancer diagnosed before baseline, 476 admitted to hospital for COPD before baseline, 951 with missing residential address at recruitment, 779 with missing information on covariates, and 1 477 for whom less than 80% of residential addresses history available from 1971 until the end of follow-up. Of the 52 799 remaining subjects, 1 786 (3·4%) were admitted to hospital for COPD for the first time between baseline and 27 June 2006, with an average follow-up of 9.9 years. The overall incidence rate was 3.4 cases per 1000 person-years. The distribution of baseline covariates and co-morbid conditions is shown in Table 1.

The distribution of traffic proxies is shown in Table 2. The estimated 35-year mean levels of NO_2 and NO_x at residential addresses varied widely (Figure 1). The Spearman rank correlation coefficient (r_s) between the 35- and 25-year mean NO_2/NO_x was 0.98/0.97, r_s between the 35- and the 15-year levels was 0.92/0.90, and between 25- and 15-year 0.96/0.95. The 35-year mean NO_2 and NO_x levels were highly correlated (0.91). Traffic load within 200m and living within 50m of a major road at recruitment address were moderately correlated with the 35-years mean NO_2 and NO_x levels, with r_s of 0.49/0.45 and 0.53/0.45, respectively, and even more weakly correlated with the estimated 1-year mean NO_2 and NO_x levels at the baseline (1993-1997) with r_s of 0.37/0.30 and 0.36/0.39, respectively.

We found significant positive associations between all air pollution proxies and COPD incidence in a model adjusted for age (Table 3). The HRs were attenuated after adjustment for smoking but were significant for 35-years' exposure to NO_2 and NO_x and for 25-years' exposure to NO_2, whereas HRs related for 15-years' exposure, a major road within 50m, or traffic load within 200m, did not retain statistical significance. After further adjustment for occupation, educational level, BMI, and fruit intake, significant associations with COPD incidence remained for the 35- and 25-year mean levels of NO_2 (1.08; 1.02-1.14 and 1.07; 1.01-1.06) and 35-years mean level of NO_x (1.05; 1.01-1.10), while weak positive associations were observed with the 25-year mean level of NO_x, 15-year mean levels of NO_2 and NO_x, and baseline residence traffic proxies. The associations with NO_2 were stronger than those with NO_x. Additional adjustment for gender, physical activity, alcohol consumption, and vegetable consumption did not substantially change the risk estimates.

We found slightly stronger associations between 35-year mean NO_2 level and COPD incidence among men, people eating < 240g/day of fruit, and obese patients, although no significant modification of the effect of NO_2 was observed by any of the baseline characteristics (Table 4).

We detected modifications of borderline significance of the association between NO_2 levels and COPD by asthma (Wald test for interaction $p = 0.10$) and diabetes ($p = 0.08$) (Table 4). In COPD patients with ischaemic, other heart disease, or stroke, the associations with NO_2 levels were slightly stronger than in people without these co-morbid conditions, but not significantly different.

Discussion

Our investigation resulted in two novel findings. First, we found positive associations between 35-years' exposure to NO_2 and NO_x at residential addresses and the incidence of

COPD, defined as first-ever hospital admission for COPD, in a cohort of elderly Danish adults. Secondly, the effect of air pollution was strongest in people with diabetes and asthma. This is the first study to relate the incidence of COPD, assessed as first hospital admission, to long-term exposure to air pollution. Our results are in agreement with those of cross-sectional studies that linked long-term exposure to air pollution to a self-reported diagnosis of COPD[10-12] and decreased lung function.[11,14] The results of our study, with detailed assessment of long-term exposure before hospital admission for COPD, together with the finding that reductions in air pollution over time contribute to improving lung function and respiratory symptoms,[17,18] and studies in which chronic exposure to air pollution was identified as a risk factor in mortality from respiratory conditions including COPD mortality,[7-9] strengthen the conclusion that air pollution is a causal agent in development of COPD.

The strongest association with COPD incidence was found with the longest exposure (Table 3) reinforcing the conclusion that exposure over a long period, perhaps over a whole life, is relevant for the development of chronic lung diseases such as COPD. Our results are not directly comparable to those of other studies, in which a variety of surrogates for air pollution and exposure windows were used. Because of the absence of historical address data, most studies used single-year air pollution proxies assessed at the residential address at the time of the event, including modeled NO_2[12] or traffic density.[12,14,15] Schikowski et al. reported a stronger association with the prevalence of COPD with 5-year than with 1-year NO_2 means.[11] Karakatsani et al. found an effect of 5-year but none of 20-year mean air pollution levels but attributed this finding to possible bias in self-reported address history.[10] A longitudinal study with 9-years' follow-up,[16] and Gotschi et al. found no association between lung function and modeled NO_2.[15] Some of the discrepancies in the reported effects of exposure to air pollution on COPD and lung function might be not only due to the variable, often short periods of exposure assessment. It has recently been suggested that assessment of lung function by the

usual forced expiratory volume in the first second or the ratio to forced vital capacity without measurement after administration of a bronchodilator, is insufficiently sensitive to detect COPD incidence in epidemiological studies.[21]

COPD is a chronic disease of complex phenotype and recurring symptoms, and it is difficult to define its onset, as well as its presence or absence at some point of time. Studies of air pollution and COPD prevalence[10-12] utilized self-reported symptoms or diagnose of COPD, which are subject to recall and information bias. The use of the first-ever hospital admission for COPD, assessed objectively from nationwide register, is thus appealing, and facilitates the first data on COPD incidence with respect to air pollution. However, as only a fraction of COPD patients are hospitalized, and COPD is often undiagnosed for many years, the first-ever hospital admission for COPD is not likely an accurate marker of COPD incidence and under represents the real COPD burden. Rather, COPD admission should be regarded as hallmark of progression of preexisting COPD into a more severe stage. A Danish revealed that the patients admitted acutely because of an COPD exacerbation, had a FEV_1 of approximately 30-40% of the predicted value in their stable condition, corresponding to GOLD standard stage 3 and 4.[22] Thus, our study examines the onset of more severe COPD, and likely represents patients with severe disease. Still, our study design with air pollution exposure information available up to 35-years prior to hospital admission for COPD, even if the real onset of COPD occurred several years prior to hospital admission, justifies the incidence interpretation of our results and facilitates inferences about causality.

Our findings corroborate the postulated biological mechanism whereby repeated inhalation injury of lung tissues by long-term exposure to air pollution contributes to progression and development of COPD, implying that the longer the exposure, the higher risk for COPD.[3] Similarly, a recent study of the effect of smoking on the development of COPD over 25 years showed that the longer people smoke, the higher their risk for COPD.[23]

We found that the traffic-related air pollutants NO_2 and NO_x are relevant for COPD development, NO_2 having the strongest effect. NO_2 is an airway irritant which even at the low concentrations found in everyday life can cause respiratory tract infections by interacting with the immune system and may play a role in lung inflammation,[24] We cannot conclude from our study that NO_2 is of pathological significance in COPD or just an indicator of other harmful pollutants originating from traffic, especially particles. The biological effects of NO_2 are uncertain and controversial, with limited experimental evidence supporting the notion that long-term exposures can cause COPD,[25] whereas the role of particles seems to be better understood. The particles deposited in the airways can trigger a local inflammatory response in lung tissue and also a systemic inflammatory response.[3,5] As gases and particles from motor vehicle emissions are mixed in urban air, the harmful effects after inhalation might represent the synergistic effect of the effect of several pollutants. In any case, sufficient data,[8,9,12,14,17,18] including the results of this study, provide evidence that traffic-related urban air pollution contributes to the development of COPD and that reductions in traffic emissions would be beneficial for public health.

Smoking is the main risk factor for COPD,[1] as corroborated by our study (Table 1), and the effect of air pollution could be biased by inadequate adjustment for smoking. We adjusted our results for smoking status, intensity, and duration, and ETS, each of which is an independent predictor of COPD and showed that smoking explains some of the association observed in the unadjusted model (Table 3). Furthermore, we found no evidence that the association between exposure to NO_2 and COPD was modified by smoking status, as exposure estimate for nonsmokers was similar to that of the rest of the cohort (Table 4). This result refutes the possibility that the observed effect of air pollution is due to residual confounding by smoking, and supports idea that recurrent inflammatory processes induced by air pollution contribute to the development of COPD, irrespective of smoking.[1,3,5,24] Furthermore, the risk estimates

associated with exposure to NO_2 were similar for people with and without occupational exposure associated with lung disease, obviating the conclusion that the observed effect of air pollution was due to residual confounding by occupational exposure. Given the ubiquitous nature of air pollution, our findings support those of a recent review which found that the burden of COPD among nonsmokers is much greater than previously believed and that environmental factors such as air pollution probably play an important role.[1]

Our results suggest that the effect of NO_2 on COPD is modified by diabetes and asthma, as patients with these conditions had HRs five and four times larger, respectively, than the rest of the cohort (Table 4). COPD and co-morbid conditions are chronic diseases with probable onset before hospital admission. We thus cannot infer which specific tissues were affected first, and which disease was secondary complication, although the most (> 92%) hospital admissions for co-morbid conditions occurred before the admission for COPD. Our results suggest that people with asthma or diabetes are more vulnerable to the effects of air pollution, leading to increased risk of COPD. Diabetes was recently linked to air pollution in a study which showed that particles exacerbate insulin resistance by enhancing inflammation in adipose tissue, and air pollution-induced systemic inflammatory response was considered a possible link between diabetes and lung inflammation.[26] Our finding that the strongest association between exposure to NO_2 and COPD was in obese patients (Table 4) supports this mechanism. Asthma, which is associated with both air pollution[27] and an increased risk for COPD,[28] has many common risk factors and features with COPD, such as hyperactivity and inflammation.[3] It is plausible that airflow obstruction and hyper-responsiveness in people with asthma, or systemic inflammation in people with diabetes, can lead to increased susceptibility of the lung to air pollution, resulting in airway inflammation and progression of COPD.[3,25]

The main strength of this study is the objective definition of incidence of COPD as the first admission for this condition in the Danish Hospital Discharge Register, a nationwide register

of routinely collected data with no loss to follow-up. Hospital admission for COPD was evaluated to be a reliable outcome in a previous Danish cohort, as lung function and respiratory symptoms were strong predictors.[29] Another strength of this study is the large prospective cohort with address history and information on potential confounders collected before admission for COPD. As the DCH cohort was not originally designed to study COPD or air pollution, and COPD incidence, vital status, and the information on addresses used in modeling air pollution were obtained from the reliable population-based registries, the possibility of information or recall bias with respect to health outcome or differential bias with respect to exposure, is minimal.

The weakness of our study is that our primary outcome was hospital admission for COPD as primary diagnosis and not the COPD diagnose as confirmed by spirometry, making the association between exposure to of air pollution and COPD indirect. However, hospitals in Denmark hold a strong tradition of performing spirometry before discharging of COPD patients, but spirometry records are not routinely available in the hospital register, and could not be assessed for purpose of this study.[30] Furthermore, the coding of COPD diagnoses in Danish hospital register are not done by administrators, but by doctors, usually at specialist level, which together with the fact that spirometry is routinely performed at hospitalization, minimizes the diagnoses misclassification and the possibility that patients admitted to hospital for CODP were not real COPD cases.[30] Another weakness of this study is the lack of lung function measurements in our cohort, which would be relevant to associate to long-term accumulated air pollution. Finally, the weakness of this study is that despite sufficiently large cohort and long follow-up, we detected effects of weak or borderline significance, calling for caution in interpreting the strength of reported associations and replication of these results by other studies.

The dispersion models we used to assess NO_2 and NO_x levels at the addresses of study participants have been validated[31,32] and applied in Denmark[33,34] and the United States.[35] Although modeled concentrations are only surrogates of real exposures and are inevitably associated with some exposure misclassification, this is however likely to be non-differential with respect to development of COPD. A previous comparison of measured NO_2 concentrations with those calculated from a Danish dispersion model showed that misclassification was primarily of the Berkson type, typically associated with exposures predicted from the model.[33,34] This type of error is not expected to bias the estimates, although it may decrease their precision.[34] A further limitation of the exposure assessment method is that we assessed only outdoor concentrations, and lacked information on work address, commuting habits, and personal activities.

In conclusion, we report an association between long-term exposure to traffic-related air pollution and the incidence of COPD. The effect of air pollution appears to be amplified by co-existing diabetes or asthma but is not limited to these vulnerable subpopulations.

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References

1 Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;374:733-43.

2 Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. *Respirology* 2006;11:523-32.

3 Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2009;4:233-43.

4 Sint T, Donohue JF, Ghio AJ. Ambient air pollution particles and the acute exacerbation of chronic obstructive pulmonary disease. *Inhal Toxicol* 2008;20:25-9.

5 Hogg JC, van Eeden S. Pulmonary and systemic response to atmospheric pollution. *Respirology* 2009;14:336-46.

6 Kurmi OP, Semple S, Simkhada P, Smith WCS, Ayres JG. *Thorax* 2010;65:221-228.

7 Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002;360:1203-9.

8 Naess Ø, Nafstad P, Aamodt G, Claussen B, Rosland P. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *Am J Epidemiol* 2007;165:435-43.

9 Hart JE, Garshik E, Dockery DW, Smith TJ, Ryan L, Laden F. Long-term ambient multi-pollutant exposures and mortality. *Am J Respir Crit care Med.* (In press)

10 Karakatsani A, Andreadaki S, Katsouyanni K, Dimitroulis I, Trchopoulos D, Benetou V, Trichopoulou A. Air pollution in relation to manifestations of chronic pulmonary disease: a nested case-control study in Athens, Greece. *Eur J Epidemiol* 2003;18:45-53.

11 Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE, Kramer U. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respir Res* 2005;6:152.

12 Lindgren A, Stroh E, Montnemery P, Nihlen U, Jakobsson K, Axmon A. Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden. *Int J Health Geogr* 2009;8:2.

13 Sunyer J. Lung function effects of chronic exposure to air pollution. *Thorax* 2009;64:645-6.

14 Kan H, Heiss G, Rose KM, Whitsel E, Lurmann F, London SJ. Traffic exposure and lung function in adults: the Atherosclerosis Risk in Communities study. *Thorax* 2007;62:873-9.

15 Gotschi T, Sunyer J, Chinn S, de Marco R, Forsberg B, Gauderman JW, Garcia-Esteban R, Heinrich J, Jacquemin B, Jarvis D, Ponzio M, Villani S, Kunzli N. Air pollution and lung function in the European Community Respiratory Health Survey. *Int J Epidemiol* 2008;37:1349-58.

16 Pujades-Rodriguez M, McKeever T, Lewis S, Whyatt D, Britton J, Venn A. Effect of traffic pollution on respiratory and allergic disease in adults: cross-sectional and longitudinal analyses. *BMC Pulm Med* 2009;9:42.

17 Downs SH, Schindler C, Liu LJ, Keidel D, Bayer-Oglesby L, Brutsche MH, Gerbase MW, Keller R, Künzli N, Leuenberger P, Probst-Hensch NM, Tschopp JM, Zellweger JP, Rochat T, Schwartz J, Ackermann-Liebrich U; SAPALDIA Team. Reduced exposure to PM10 and attenuated age-related decline in lung function. *N Engl J Med* 2007;357:2338-47.

18 Schindler C, Keidel D, Gerbase MW, Zemp E, Bettschart R, Brändli O, Brutsche MH, Burdet L, Karrer W, Knöpfli B, Pons M, Rapp R, Bayer-Oglesby L, Künzli N, Schwartz J, Liu LJ, Ackermann-Liebrich U, Rochat T; SAPALDIA Team. Improvements in PM_{10} exposure and reduced rates of respiratory symptoms in a coho rt of Swiss adults (SAPALDIA). *Am J Respir Crit care Med* 2009;179:579-87.

19 Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health* 2007;35:432-441.

20 Jensen SS, Berkowicz R, Hansen SH, Hertel O. A Danish decision-support GIS tool for management of urban air quality and human exposures. *Transport Res Part D: Transport Environ* 2001;6:229-241.

21 Probst-Hensch NM, Curjuric I, Pierre-Olivier B. Longitudinal change of prebronchodilator spirometric obstruction and health outcomes: results from the SAPALDIA cohort. *Thorax* 2010;65:150-6.

22 Eriksen N, Hansen EF, Munch EP, Rasmussen FV, Vestbo J. Chronic obstructive pulmonary disease. Admission, course and prognosis. (Article in Danish). *Ugeskr Laeger* 2003;165:3499-502.

23 Løkke A, Lange P, Scharling H, Fabricius P, Vestbo J. developing COPD: a 25 year follow up study of the general population. *Thorax* 2006;61:935-939.

24 Wegmann M, Fehrenbach A, Heimann S, Fehrenbach H, Renz H, Garn H, Herz U. NO2-induced airway inflammation is associated with progressive airflow limitation and development of emphysema-like lesions in C57bl/6 mice. *Exp Toxicol Pathol* 2005;56:341-50.

25 Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. Critical review of the human ata on short-term nitrogen dioxide (NO2) exposures evidence for NO2 no-effect effects. *Crit Rev Toxicol* 2009;39:195-227.

26 Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S, Brook RD, Moffatt-Bruce SD, Chen LC, Rajagopalan S. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009;119:538-46.

27 Künzli N, Bridevaux PO, Liu LJ, Garcia-Esteban R, Schindler C, Gerbase MW, Sunyer J, Keidel D, Rochat T; Swiss Cohort Study on Air Pollution and Lung Diseases in Adults. Traffic-related air pollution correlates with adult-onset asthma among never-smokers. *Thorax* 2009;64:664-70.

28 Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59-65.

29 Vestbo J, Rasmussen FV. Respiratory symptoms and FEV as predictors of hospitalization and medication in the following 12 years due to respiratory disease. *Eur Respir J* 1989;2:710-715.

30 Ingebrigtsen T, Thomsen SF, Vestbo J, van der Sluis S, Kyvik KO, Silverman EK, Svartengren M, Backer V. Genetic influences on chornic obstructive pulmonary disease – A twin study. *Respir Med.* (In press)

31 Berkowicz R, Ketzel M, Jensen JJ, Hvidberg M, Raaschou-Nielsen O. Evaluation and application of OSPM for traffic pollution assessment for large number of street locations. *Environ Model Software* 2008;23:296-303.

32 Raaschou-Nielsen O, Hertel O, Vignati E, Berkowicz R, Jensen SS, Larsen VB, Lohse C, Olsen JH. An air pollution model for use in epidemiological studies: evaluation with measured levels of nitrogen dioxide and benzene. *J Expo Anal Environ Epidemiol* 2000;10:4-14.

33 Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol* 2001;153:433-443.

34 Raaschou-Nielsen O, Bak H, Sørensen M, Jensen SS, Ketzel M, Hvidberg M, Schnohr P, Tjønneland A, Overvad K, Loft S. Air Pollution from Traffic and Risk for Lung Cancer in Three Danish Cohorts. *Cancer Epidemiol Biomarkers Prev* 2010;19:1284-91.

35 Jensen SS, Larson T, Deepti KC, Kaufman JD. Modeling traffic air pollution in street canyons in New York City for intra-urban exposure assessment in the US Multi-Ethnic study of atherosclerosis and air pollution. *Atmos Environ* 2009;43:4544-4556.

Table 1. Characteristics of Diet, Cancer and Health cohort (*n* = 52 799) by incident COPD status at follow-up.

	Total *n* = 52 799	**No COPD** *n* = 51 013	**COPD** *n* = 1 786	p Value*
Baseline cohort covariates				
Median (IQR) Age (years)	56.1 (7.6)	56.0 (7.4)	58.8 (7.7)	<0.001
Males *n* (%)	25 066 (47.5)	24 269 (47.6)	797 (44.6)	<0.001
Never smoked *n* (%)	18 904 (35.8)	18 781 (36.8)	123 (6.9)	<0.001
Previously smoked *n* (%)	14 986 (28.4)	14 672 (28.8)	314 (17.6)	
Currently smoke *n* (%)	18 909 (35.8)	17 560 (34.4)	1 349 (75.5)	
Median (IQR) smoking duration (years)	32.0 (18.0)	32.0 (18.0)	39.0 (9.0)	<0.001
Median (IQR) smoking intensity (g/day)	6.0 (18.0)	5.0 (18.0)	15.0 (12.0)	<0.001
Environmental tobacco smoke *n* (%)	33 754 (63.9)	32 162 (63.0)	1 592 (89.1)	<0.001
Median (IQR) body mass index (kg/m^2)	25.5 (4.9)	25.5 (4.9)	25.0 (5.8)	<0.001
< 8 years of education *n* (%)	17 343 (32.9)	16 471 (32.3)	872 (48.9)	<0.001
8 - 10 years of education *n* (%)	24 422 (46.2)	23 721 (46.5)	701 (39.2)	
≥ 10 years of education *n* (%)	11 034 (20.9)	10 821 (21.2)	213 (11.9)	
Occupational exposure *n* (%)	14 701 (27.8)	14 038 (27.5)	663 (37.1)	<0.001
Median (IQR) fruit intake (g/day)	145.7 (165.4)	146.7 (165.8)	120.0 (144.4)	<0.001
Co-morbidities (ICD-10 Code)				
Asthma (J45-46) *n* (%)	1 171 (2.2)	874 (1.7)	297 (16.6)	<0.001
Ischemic heart disease (I20-25) *n* (%)	5 493 (10.4)	5 151 (10.1)	342 (19.1)	<0.001
Other heart disease (I42-I50) *n* (%)	5 706 (10.8)	5 351 (10.5)	355 (19.9)	<0.001
Stroke (I60-I63) *n* (%)	2 706 (5.1)	2 559 (5.0)	147 (8.2)	<0.001
Diabetes (E10-14) *n* (%)	2 141 (4.1)	2 021 (4.0)	120 (6.7)	<0.001

COPD, chronic obstructive respiratory disease; IQR, interquartile range.
* For Kruskal-Wallis test or χ^2 test comparing two/three groups between 'No COPD' and 'COPD' columns.

Table 2. Description of proxies of exposure to air pollution in the Diet, Cancer and Health cohort (*n* = 52 799), total and by incident COPD status at follow-up.

		Total			**COPD**		
Length of		*n* = 52 799			*n* = 1 786		
Exposure	*Air pollution proxy*	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR
35 years[*]	NO_2 ($\mu g/m^3$)	17.0 (5.2)	15.3	5.8	18.1 (5.6)	16.8	6.6
(1971-)	NO_x ($\mu g/m^3$)	28.2 (21.0)	21.6	12.4	31.5 (23.3)	23.5	16.2
25 years	NO_2 ($\mu g/m^3$)	17.8 (6.0)	15.5	6.4	19.3 (6.5)	17.6	7.2
(1981-)	NO_x ($\mu g/m^3$)	29.4 (24.1)	21.5	12.6	33.2 (27.3)	24.2	16.9
15 years	NO_2 ($\mu g/m^3$)	17.1 (6.3)	14.5	6.3	18.7 (6.9)	16.9	7.5
(1991-)	NO_x ($\mu g/m^3$)	27.8 (24.7)	19.3	11.6	31.9 (28.2)	22.6	16.6
1 year	Traffic load[†] 200m						
mean	(10^3 vehicle km/day)	4.7 (5.4)	2.6	5.8	5.3(5.7)	3.5	6.5
(baseline)	Major road[‡] 50m *n* (%)	4 310 (8.2%)			187 (10.5%)		

COPD, chronic obstructive respiratory disease; SD, standard deviation.; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen oxides;

[*]35, 25, and 15 years defined as weighted mean of annual NO_2 and NO_x concentrations from 1971, 1981, and 1991, respectively until event, censoring. or 27 June 2006; [†] Total number of km traveled within 200m (sum of product of street length and traffic density for each road);
[‡]Road with annual traffic density of 10 000 vehicles or more.

Table 3. Association between traffic-related air pollution and COPD incidence (n = 1 797) among 52 799 Diet, Cancer and Health cohort participants.

	Adjusted for age	Adjusted for age, smoking status, duration, intensity and environmental tobacco smoke	Fully adjusted*
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
35-year mean (1971-event, censoring, or 27 June 2006)			
NO_2† (µg/m^3)	1.22 (1.15-1.29)	1.08 (1.02-1.14)	1.08 (1.02-1.14)
NO_x† (µg/m^3)	1.16 (1.11-1.22)	1.05 (1.01-1.10)	1.05 (1.01-1.10)
25-year mean (1981- event, censoring, or 27 June 2006)			
NO_2† (µg/m^3)	1.20 (1.13-1.27)	1.06 (1.01-1.13)	1.07 (1.01-1.06)
NO_x† (µg/m^3)	1.14 (1.09-1.19)	1.04 (0.99-1.09)	1.04 (0.99-1.09)
15-year mean (1991- event, censoring, or 27 June 2006)			
NO_2† (µg/m^3)	1.18 (1.11-1.24)	1.05 (0.99-1.11)	1.05 (1.00-1.11)
NO_x† (µg/m^3)	1.12 (1.07-1.17)	1.03 (0.99-1.08)	1.03 (0.99-1.09)
1-year mean at cohort baseline (1993-1997)			
Major road‡ within 50m	1.25 (1.07-1.45)	1.05 (0.90-1.22)	1.04 (0.89-1.21)
Traffic load§ within 200m	1.10 (1.06-1.14)	1.01 (0.98-1.05)	1.01 (0.97-1.05)

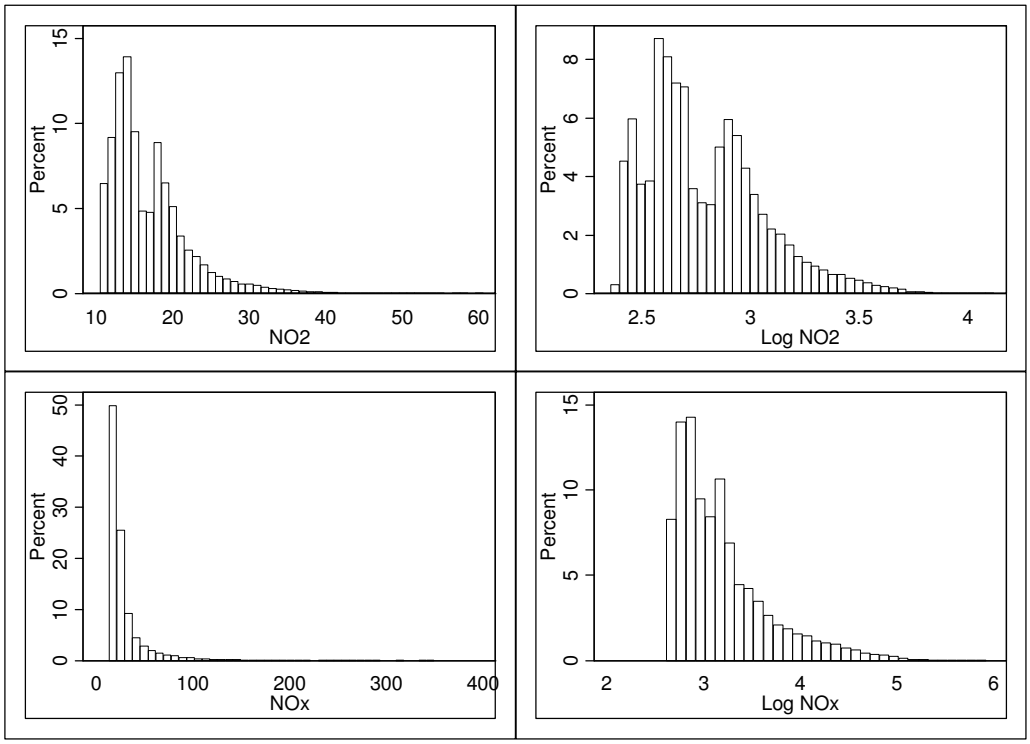
COPD, chronic obstructive respiratory disease; HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; *Adjusted for smoking status, smoking duration, smoking intensity, environmental tobacco smoke, body mass index, educational level, occupational exposure, and fruit consumption; † Linear trend per interquartile range; ‡ Road with annual traffic density of 10 000 vehicles or more; § Total number of km traveled within 200m (sum of product of street length and traffic density for each road).

Table 4. Modification of associations* between NO_2 (per interquartile range (5.8 µg/m^3) of 35-year mean, 1971-end of follow-up) and COPD incidence (n = 1 797) by baseline characteristics and co-morbid conditions of 52 799 Diet, Cancer, and Health cohort participants.

Covariate Co-morbid condition	*Covariate Levels*	n_{cases}	***Incident rate*** †	**HR (95% CI)**	***p-value*** ‡
Gender	Male	797	3.2	1.07 (0.98-1.16)	
	Female	989	3.6	1.05 (0.97-1.13)	0.81
Smoking status	Currently smoke	1349	7.1	1.06 (1.06-1.31)	
	Previously smoked	314	2.1	1.14 (0.87-1.42)	
	Never smoked	123	0.6	1.10 (0.86-1.33)	0.78
Occupational exposure	Yes	663	4.5	1.08 (0.98-1.19)	
	No	1123	2.9	1.07 (1.00-1.15)	0.96
Educational level	< 8 years	872	5.0	1.08 (1.00-1.18)	
	8 - 10 years	701	2.9	1.07 (0.97-1.17)	
	≥ 10 years	213	1.9	1.08 (0.91-1.29)	0.94
Fruit consumption	< 240g	1445	3.7	1.09 (1.02-1.15)	
	≥ 240g	339	2.6	1.04 (0.91-1.19)	0.55
Body mass index	Underweight (<18.5 kg/m^2)	48	12.8	1.01 (0.69-1.49)	
	Normal (18.5-24 kg/m^2)	841	3.7	1.03 (0.95-1.13)	
	Overweight (25-29 kg/m^2)	624	2.9	1.04 (0.95-1.15)	
	Obese(≥ 30 kg/m^2)	273	3.6	1.21 (1.05-1.40)	0.34
Asthma	*Has COPD*	297	29.3	1.19 (1.03-1.38)	
	No COPD	1489	2.9	1.05 (0.98-1.12)	0.10
Ischemic heart disease	*Has COPD*	342	6.4	1.10 (0.96-1.26)	
	No COPD	1444	3.1	1.08 (1.01-1.15)	0.81
Other heart disease	*Has COPD*	355	6.4	1.11 (0.98-1.26)	
	No COPD	1431	3.1	1.07 (1.00-1.13)	0.57
Stroke	*Has COPD*	147	5.6	1.10 (0.90-1.35)	
	No COPD	1639	3.3	1.08 (1.02-1.14)	0.85
Diabetes	*Has COPD*	120	11.0	1.29 (1.05-1.60)	
	No COPD	1666	3.3	1.06 (1.00-1.13)	0.08

COPD, chronic obstructive respiratory disease; HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide;
*Adjusted for smoking status, smoking duration, smoking intensity, body mass index, educational level, occupational exposure, and fruit consumption; † Crude incident rate per 1000 person-years; ‡ For Wald test for interaction.

Figure 1. Distribution of 35-year accumulated mean levels of NO_2 and NO_x at residences of 52 799 Diet, Cancer and Health cohort members (original-left, log-transformed-right)


Percent
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30
40
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NO2
Percent
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2
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Log NO2
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NOx
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2
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4
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Log NOx

Online Data Supplement

Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study

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AirGIS Model

AirGIS model,[E1] based on a geographical information system (GIS), is used for estimating traffic-related air pollution and has high temporal (an hour) and spatial (individual address) resolution. AirGIS calculates air pollution at a location as the sum of three contributors: (1) local air pollution from street traffic, calculated with the Operational Street Pollution Model[E2] (OSPM) from data on traffic (intensity and type), emission factors for each vehicle type and EURO class, street and building geometry, and meteorology; (2) urban background, calculated from a simplified urban background (SUB) procedure[E3] that takes into account urban vehicle emission density, city dimensions (transport distance), and average building height (initial dispersion height); and (3) regional background, estimated from trends at rural monitoring stations and from national vehicle emissions.[E4] Input data for the AirGIS system come from various sources: a GIS-based national street and traffic database, including construction year and traffic data for the period 1960–2005,[E5] and a database on emission factors for the Danish car fleet,[E6,E7] with data on light- and heavy-duty vehicles dating back to 1960, built and entered into the emission module of the OSPM. A national GIS database with building footprints supplemented with construction year and building height from the national building and dwelling register, national survey and cadastre data-bases, and a national terrain-evaluation model, provided the correct street geometry for a given year at a given address. With a geocoded address and a year, the starting point is specified in place and time, and the AirGIS system automatically generates street configuration data for the OSPM, including street orientation, street width, building heights in wind sectors, traffic intensity and type, and the other data required for the model. The AirGIS system has been successfully validated[E3,E8] and used in several studies.[E9-E11]

References:

E1 Jensen SS, Berkowicz R, Hansen SH, Hertel O. A Danish decision-support GIS tool for management of urban air quality and human exposures. *Transport Res Part D: Transport Environ* 2001;6:229–41.

E2 Berkowicz R. OSPM - A parameterised street pollution model. *Environ Monit Assess* 2000; **65**:323–31.

E3 Berkowicz R, Ketzel M, Jensen SS, Hvidberg M, Raaschou-Nielsen O. Evaluation and application of OSMP for traffic pollution assessment for large number of street locations. *Environ Model Software* 2008; **23**:296–303.

E4 Jensen SS. Background concentrations for use in the Operational Street Pollution Model (OSPM). Roskilde, National Environmental Research Institute, Aarhus University. NERI Technical Reports. 1998; **234**:1–107.

E5 Jensen SS, Hvidberg M, Pedersen J, et al. GIS-based national street and traffic data base 1960-2005 (In Danish; English summary). Roskilde, National Environmantal Research Institute, Aarhus University. NERI Technical Reports. 2009; **678**:1–73.

E6 Berkowitz R, Winther M, Ketzel M. Traffic pollution modeling and emission data. *Environ Model Software* 2006;21:454–60.

E7 Ketzel M, Omstedt G, Johansson C, et al. Estimation and validation of $PM_{2.5}$/PM_{10} exhaust and non-exhaust emission factors for practical street pollution modeling. Atmos Environ 2007; **41**:9370–85.

E8 Raaschou-Nielsen O, Hertel O, Vignati E et al. An air pollution model for use in epidemiological studies: evaluation with measured levels of nitrogen dioxide and benzene. *J Expo Anal Environ Epidemiol* 2000; **10**:4–14.

E9 Jensen SS, Larson T, Deepti KC, Kaufman JD. Modeling traffic air pollution in street canyons in New York City for intra-urban exposure assessment in the US multi-ethnic study of atherosclerosis and air pollution. *Atmos Environ* 2009; **43**:4544–56.

E10 Hertel O, Jensen SS, Andersen HV et al. Human exposure to traffic pollution. Experience from Danish studies. *Pure Appl Chem* 2001; **73**:137–145.

E11 Hertel O, Hvidberg M, Ketzel M, et al. A proper choice of route significantly reduces air pollution exposure–a study on bicycle and bus trips in urban streets. *Sci Tot Environ* 2008; **389**:58–78.