

Chronic Obstructive Pulmonary Disease and Long-Term Exposure to Traffic-related Air Pollution

A Cohort Study

Zorana J. Andersen¹, Martin Hvidberg², Steen S. Jensen², Matthias Ketzel², Steffen Loft³, Mette Sørensen¹, Anne Tjønneland¹, Kim Overvad^{4,5}, and Ole Raaschou-Nielsen¹

¹Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; ²National Environmental Research Institute, Aarhus University, Roskilde, Denmark; ³Department of Environmental Health, University of Copenhagen, Copenhagen, Denmark; ⁴School of Public Health, Aarhus University, Aarhus, Denmark; ⁵Centre for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

Rationale: Short-term exposure to air pollution has been associated with exacerbation of chronic obstructive pulmonary 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.

Methods: 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 (NO₂) 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 comorbid conditions, including asthma, diabetes, or cardiovascular disease.

Measurements and 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 NO₂ level (hazard ratio, 1.08; 95% confidence interval, 1.02–1.14, per interquartile range of 5.8 µg/m³), with stronger associations in subjects with diabetes (1.29; 1.05–1.50) 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.

Keywords: COPD; air pollution; hospital admission; asthma; diabetes

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 believed 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. Compel-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Short-term exposure to air pollution has been associated with exacerbation of chronic obstructive pulmonary disease (COPD). 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, using several novel approaches: use of 35 years accumulated exposure of modeled levels of NO₂, use of objective measure of COPD incidence in terms of the first-ever hospital admission for COPD, and assessment of the role of comorbid conditions (asthma and diabetes) in modifying the effect of air pollution on COPD.

ling epidemiological evidence has established that exposure over several days to elevated levels of air pollution exacerbates preexisting COPD, resulting in increased morbidity and mortality (4). Solid evidence is lacking, however, 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 multipollutant models and improved control for occupational exposures (9). Several studies have reported links between high levels of air pollution and the prevalence of COPD (10–12), and none to date have studied COPD incidence. Impaired lung function, an

(Received in original form June 19, 2010; accepted in final form September 23, 2010)

Supported by The Danish Research Council.

Correspondence and requests for reprints should be addressed to Zorana J. Andersen, Ph.D. Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark. E-mail: zorana@cancer.dk

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

Am J Respir Crit Care Med Vol 183, pp 455–461, 2011

Originally Published in Press as DOI: 10.1164/rccm.201006-0937OC on September 24, 2010
Internet address: www.atsjournals.org

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 as first-ever hospital admission for COPD, in a prospective cohort of 57,053 Danish adults with detailed residential address history and information on comorbidity, 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 study consisting of 57,053 people aged 50 to 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 (International Classification of Diseases, 10th revision: J40–44) asthma (J45–46), ischemic 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. Comorbidity (with asthma, ischemic 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 (NO₂) and nitrogen oxides (NO_x) with the Danish AirGIS dispersion modeling system (20), described in detail in the online data supplement. Annual mean NO₂ 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 NO₂ 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 NO₂ 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 $\geq 10,000$ vehicles/d) within a 50 m radius, and traffic load, defined as the total number of kilometers driven by vehicles within a 200 m 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, educational level, and fruit consumption, all defined as shown in Table 1. We also evaluated other confounders, including sex, alcohol consumption, physical activity, and vegetable consumption. Levels of NO₂ 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 1 g, a cheroot or a pipe to 3 g, and a cigar to 5 g 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 h/d. The potential effect modifiers of an association between a traffic proxy and COPD incidence, in terms of baseline characteristics and comorbid conditions, were evaluated by introducing interaction terms into the model, and were 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 address history was available from 1971 until the end of follow-up. Of the 52,799 remaining subjects, 1,786 (3.4%) were admitted to the 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 1,000 person-years. The distribution of baseline covariates and comorbid conditions is shown in Table 1.

The distribution of traffic proxies is shown in Table 2. The estimated 35-year mean levels of NO₂ and NO_x at residential addresses varied widely (Figure 1). The Spearman rank correlation coefficient (r_s) between the 35- and 25-year mean NO₂/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-years was 0.96/0.95. The 35-year mean NO₂ and NO_x levels were highly correlated (0.91). Traffic load within 200 m and living within 50 m of a major road at recruitment address were moderately correlated with the 35-year mean NO₂ 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 NO₂ 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-year exposure to NO₂ and NO_x and for 25-year exposure to NO₂, whereas HRs related for 15-year exposure, a major road within 50 m, or traffic load within 200 m did not retain statistical significance. After further

TABLE 1. CHARACTERISTICS OF DIET, CANCER, AND HEALTH COHORT (N = 52,799) BY INCIDENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE 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, yr | 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, yr | 32.0 (18.0) | 32.0 (18.0) | 39.0 (9.0) | <0.001 |
| Median (IQR) smoking intensity, g/d | 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 yr of education, n (%) | 17,343 (32.9) | 16,471 (32.3) | 872 (48.9) | <0.001 |
| 8–10 yr of education, n (%) | 24,422 (46.2) | 23,721 (46.5) | 701 (39.2) | |
| ≥ 10 yr 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/d | 145.7 (165.4) | 146.7 (165.8) | 120.0 (144.4) | <0.001 |
| Comorbidities (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–E14), n (%) | 2,141 (4.1) | 2,021 (4.0) | 120 (6.7) | <0.001 |

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICD-10 = International Classification of Diseases, 10th revision; IQR = interquartile range.

* For Kruskal-Wallis test or χ^2 test comparing two/three groups between “No COPD” and “COPD” columns.

adjustment for occupation, educational level, body mass index, and fruit intake, significant associations with COPD incidence remained for the 35- and 25-year mean levels of NO₂ (1.08; 1.02–1.14 and 1.07; 1.01–1.13) and 35-year mean level of NO_x (1.05; 1.01–1.10), whereas weak positive associations were observed with the 25-year mean level of NO_x, 15-year mean levels of NO₂ and NO_x, and baseline residence traffic proxies. The associations with NO₂ were stronger than those with NO_x. Additional adjustment for sex, physical activity, alcohol consumption, and vegetable consumption did not substantially change the risk estimates.

We found slightly stronger associations between 35-year mean NO₂ level and COPD incidence among men, people eating less than 240 g/d of fruit, and obese patients, although no

significant modification of the effect of NO₂ was observed by any of the baseline characteristics (Table 4).

We detected modifications of borderline significance of the association between NO₂ levels and COPD by asthma (Wald test for interaction $P = 0.10$) and diabetes ($P = 0.08$) (Table 4). In patients with COPD with ischemic, other heart disease, or stroke, the associations with NO₂ levels were slightly stronger than in people without these comorbid conditions, but not significantly different.

DISCUSSION

Our investigation resulted in two novel findings. First, we found positive associations between 35-year exposure to NO₂ and

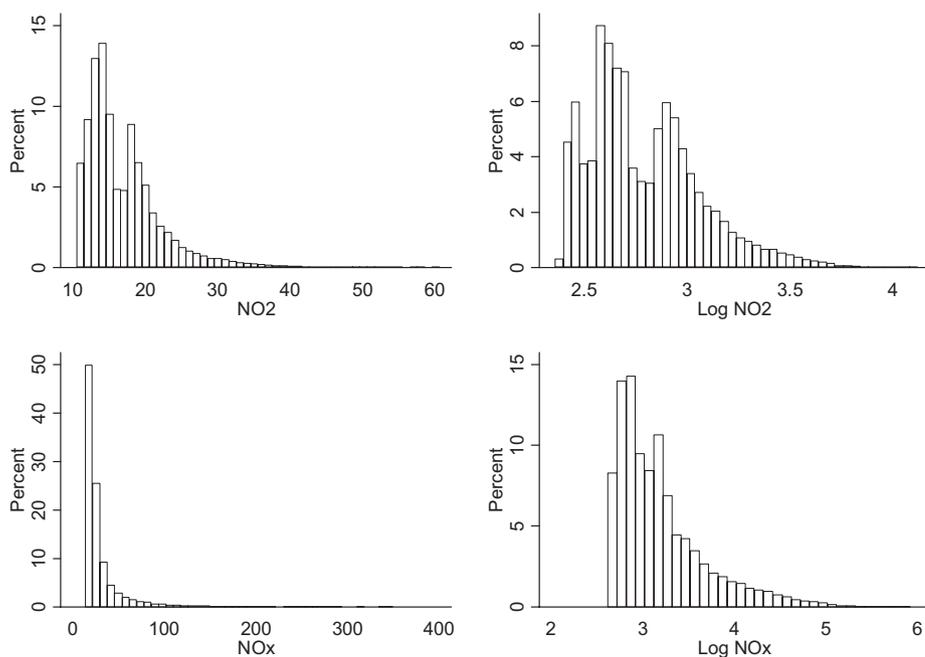


Figure 1. Distribution of 35-year accumulated mean levels of nitrogen dioxide (NO₂) and nitrogen oxides (NO_x) at residences of 52,799 Diet, Cancer, and Health cohort members (left panels, original; right panels, log-transformed).

TABLE 2. DESCRIPTION OF PROXIES OF EXPOSURE TO AIR POLLUTION IN THE DIET, CANCER, AND HEALTH COHORT (N = 52,799), TOTAL AND BY INCIDENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE STATUS AT FOLLOW-UP

| Length of Exposure* | Air Pollution Proxy | Total (n = 52,799) | | | COPD (n = 1,786) | | |
|----------------------|---|--------------------|-------------|------|------------------|------------|------|
| | | Mean (SD) | Median | IQR | Mean (SD) | Median | IQR |
| 35 yr (1971-) | NO ₂ , μg/m ³ | 17.0 (5.2) | 15.3 | 5.8 | 18.1 (5.6) | 16.8 | 6.6 |
| | NO _x , μg/m ³ | 28.2 (21.0) | 21.6 | 12.4 | 31.5 (23.3) | 23.5 | 16.2 |
| 25 yr (1981-) | NO ₂ , μg/m ³ | 17.8 (6.0) | 15.5 | 6.4 | 19.3 (6.5) | 17.6 | 7.2 |
| | NO _x , μg/m ³ | 29.4 (24.1) | 21.5 | 12.6 | 33.2 (27.3) | 24.2 | 16.9 |
| 15 yr (1991-) | NO ₂ , μg/m ³ | 17.1 (6.3) | 14.5 | 6.3 | 18.7 (6.9) | 16.9 | 7.5 |
| | NO _x , μg/m ³ | 27.8 (24.7) | 19.3 | 11.6 | 31.9 (28.2) | 22.6 | 16.6 |
| 1 yr mean (baseline) | Traffic load [†] 200 m (10 ³ vehicle km/d) | 4.7 (5.4) | 2.6 | 5.8 | 5.3 (5.7) | 3.5 | 6.5 |
| | Major road [‡] 50 m n (%) | | 4,310 (8.2) | | | 187 (10.5) | |

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; SD = standard deviation.

* 35, 25, and 15 yr defined as weighted mean of annual NO₂ and NO_x concentrations from 1971, 1981, and 1991, respectively, until event, censoring, or 27 June 2006.

[†] Total number of kilometers traveled within 200 m (sum of product of street length and traffic density for each road).

[‡] Road with annual traffic density of 10,000 vehicles or more.

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. Second, 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 NO₂ (12) or traffic density (12, 14, 15). Schikowski and colleagues reported a stronger association with the prevalence of COPD with 5-year than with 1-year NO₂ means (11). Karakatsani and colleagues 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-year follow-up (16) and Gotschi and colleagues found no association between lung function and modeled NO₂ (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 FEV₁ or the ratio to FVC without measurement after administration of a bronchodilator is insufficiently sensitive to detect COPD incidence in epidemiological studies (21).

TABLE 3. ASSOCIATION BETWEEN TRAFFIC-RELATED AIR POLLUTION AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE 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* |
|--|------------------|--|------------------|
| 35-yr mean (1971 to 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-yr mean (1981 to 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 (1.01–1.13) |
| NO _x , [†] μg/m ³ | 1.14 (1.09–1.19) | 1.04 (0.99–1.09) | 1.04 (0.99–1.09) |
| 15-yr mean (1991 to 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 (0.97–1.09) |
| 1-yr mean at cohort baseline (1993–1997) | | | |
| Major road [‡] within 50 m | 1.25 (1.07–1.45) | 1.05 (0.90–1.22) | 1.04 (0.89–1.21) |
| Traffic load [§] within 200 m | 1.10 (1.06–1.14) | 1.01 (0.98–1.05) | 1.01 (0.97–1.05) |

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CI = confidence interval; HR = hazard ratio; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides.

Data are presented as HR (95% CI).

* 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 kilometers traveled within 200 m (sum of product of street length and traffic density for each road).

TABLE 4. MODIFICATION OF ASSOCIATIONS BETWEEN NO₂ AND COPD INCIDENCE (N = 1,797) BY BASELINE CHARACTERISTICS AND COMORBID CONDITIONS OF 52,799 DIET, CANCER, AND HEALTH COHORT PARTICIPANTS

| Covariate | Comorbid Condition | Covariate Levels | No. of Cases | Incident Rate* | HR (95% CI) | P Value† |
|------------------------|--------------------|---|--------------|----------------|------------------|----------|
| Sex | | Male | 797 | 3.2 | 1.07 (0.98–1.16) | 0.81 |
| | | Female | 989 | 3.6 | 1.05 (0.97–1.13) | |
| Smoking status | | Currently smoke | 1,349 | 7.1 | 1.06 (0.81–1.31) | 0.78 |
| | | Previously smoked | 314 | 2.1 | 1.14 (0.87–1.42) | |
| | | Never smoked | 123 | 0.6 | 1.10 (0.86–1.33) | |
| Occupational exposure | | Yes | 663 | 4.5 | 1.08 (0.98–1.19) | 0.96 |
| | | No | 1,123 | 2.9 | 1.07 (1.00–1.15) | |
| Educational level | | < 8 yr | 872 | 5.0 | 1.08 (1.00–1.18) | 0.94 |
| | | 8–10 yr | 701 | 2.9 | 1.07 (0.97–1.17) | |
| | | ≥ 10 yr | 213 | 1.9 | 1.08 (0.91–1.29) | |
| Fruit consumption | | < 240 g | 1,445 | 3.7 | 1.09 (1.02–1.15) | 0.55 |
| | | ≥ 240 g | 339 | 2.6 | 1.04 (0.91–1.19) | |
| Body mass index | | Underweight (< 18.5 kg/m ²) | 48 | 12.8 | 1.01 (0.69–1.49) | 0.34 |
| | | 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) | |
| Asthma | | Has COPD | 297 | 29.3 | 1.19 (1.03–1.38) | 0.10 |
| | | No COPD | 1,489 | 2.9 | 1.05 (0.98–1.12) | |
| Ischemic heart disease | | Has COPD | 342 | 6.4 | 1.10 (0.96–1.26) | 0.81 |
| | | No COPD | 1,444 | 3.1 | 1.08 (1.01–1.15) | |
| Other heart disease | | Has COPD | 355 | 6.4 | 1.11 (0.98–1.26) | 0.57 |
| | | No COPD | 1,431 | 3.1 | 1.07 (1.00–1.13) | |
| Stroke | | Has COPD | 147 | 5.6 | 1.10 (0.85–1.35) | 0.85 |
| | | No COPD | 1,639 | 3.3 | 1.08 (1.02–1.14) | |
| Diabetes | | Has COPD | 120 | 11.0 | 1.29 (1.05–1.50) | 0.08 |
| | | No COPD | 1,666 | 3.3 | 1.06 (1.00–1.13) | |

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CI = confidence interval; HR = hazard ratio; NO₂ = nitrogen dioxide.

Associations adjusted for smoking status, smoking duration, smoking intensity, body mass index, educational level, occupational exposure, and fruit consumption. NO₂ per interquartile range (5.8 μg/m³) of 35-yr mean, 1971 to end of follow-up.

* Crude incident rate per 1,000 person-years.

† For Wald test for interaction.

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) used self-reported symptoms or diagnosis 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 patients with COPD 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 study revealed that the patients admitted acutely because of a COPD exacerbation had an FEV₁ of approximately 30% to 40% of the predicted value in their stable condition, corresponding to Global Initiative for Chronic Obstructive Lung Disease (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 before hospital admission for COPD, even if the real onset of COPD occurred several years before 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 the 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 NO₂ and NO_x are relevant for COPD development, NO₂ having the strongest effect. NO₂ 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 NO₂ is of pathological significance in COPD or just an indicator of other harmful pollutants originating from traffic, especially particles. The biological effects of NO₂ 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

NO₂ 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 the 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 NO₂ 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 NO₂ 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 comorbid conditions are chronic diseases with probable onset before hospital admission. We thus cannot infer which specific tissues were affected first, and which disease was a secondary complication, although the most (> 92%) hospital admissions for comorbid 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 showing 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 NO₂ 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 hyperresponsiveness 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 Danish Diet, Cancer, and Health 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 diagnosis as confirmed by spirometry, making the association between exposure to air pollution and COPD indirect. However, hospitals in Denmark hold a strong tradition of performing spirometry before discharging of patients with COPD, 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 the Danish hospital register are not done by administrators, but by doctors, usually at the specialist level, which, together with the fact that spirometry is routinely performed at hospitalization, minimizes the diagnosis misclassification and the possibility that patients admitted to hospital for COPD 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 NO₂ 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 likely to be nondifferential with respect to development of COPD. A previous comparison of measured NO₂ 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 coexisting diabetes or asthma but is not limited to these vulnerable subpopulations.

Author Disclosure: Z.J.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.S.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.R.-N. is employed by the Danish Cancer Society as the head of the research department.

References

1. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;374:733–743.
2. Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. *Respirology* 2006;11:523–532.
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;4:233–243.
4. Sint T, Donohue JF, Ghio AJ. Ambient air pollution particles and the acute exacerbation of chronic obstructive pulmonary disease. *Inhal Toxicol* 2008;20:25–29.
5. Hogg JC, van Eeden S. Pulmonary and systemic response to atmospheric pollution. *Respirology* 2009;14:336–346.
6. Kurmi OP, Semple S, Simkhada P, Smith WCS, Ayres JG. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. *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;360:1203–1209.
8. Naess Ø, Nafstad P, Aamodt G, Clausen 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;165:435–443.
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* 2010;183:73–78.
 10. Karakatsani A, Andreadaki S, Katsouyanni K, Dimitroulis I, Trichopoulos 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;64:645–646.
 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;62:873–879.
 15. Gotschi T, Sunyer J, Chinn S, de Marco R, Forsberg B, Gauderman JW, Garcia-Esteban R, Heinrich J, Jacquemin B, Jarvis D, *et al.* Air pollution and lung function in the European Community Respiratory Health Survey. *Int J Epidemiol* 2008;37:1349–1358.
 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, *et al.* SAPALDIA Team. Reduced exposure to PM₁₀ and attenuated age-related decline in lung function. *N Engl J Med* 2007;357:2338–2347.
 18. Schindler C, Keidel D, Gerbase MW, Zemp E, Bettschart R, Brändli O, Brutsche MH, Burdet L, Karrer W, Knöpfli B, *et al.* SAPALDIA Team. Improvements in PM₁₀ exposure and reduced rates of respiratory symptoms in a cohort of Swiss adults (SAPALDIA). *Am J Respir Crit Care Med* 2009;179:579–587.
 19. Tjønneland 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. *Transp Res Part D Transp 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;65:150–156.
 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;165:3499–3502.
 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;56:341–350.
 25. Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. Critical review of the human data 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, Deuiulis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S, *et al.* Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009;119:538–546.
 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;64:664–670.
 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 chronic obstructive pulmonary disease: a twin study. *Respir Med* 2010;104:1890–1895.
 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 Softw* 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;19:1284–1291.
 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.