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<http://dx.doi.org/10.1289/ehp.1408762>

Received: 1 June 2014

Accepted: 24 March 2015

Advance Publication: 27 March 2015

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Long-Term Ambient Residential Traffic–Related Exposures and Measurement Error–Adjusted Risk of Incident Lung Cancer in the Netherlands Cohort Study on Diet and Cancer

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Short title: Long-term air pollution exposure and lung cancer

Acknowledgments: Supported by NIH NIEHS / R01 ES009411

Competing financial interests: The authors declare they have no competing interests.

Abstract

Background: The International Agency for Research on Cancer (IARC) recently declared air pollution carcinogenic to humans. However, no study of air pollution and lung cancer to date has incorporated adjustment for exposure measurement error, and few have examined specific histological subtypes.

Objectives: Assess the association of air pollution and incident lung cancer in the Netherlands Cohort Study on Diet and Cancer and the impact of measurement error on these associations.

Methods: The cohort was followed 1986-2003 and 3,355 incident cases were identified. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals, for long-term exposures to NO₂, black smoke (BS), PM_{2.5}, and measures of roadway proximity and traffic volume, adjusted for potential confounders. Information from a previous validation study was used to correct the effect estimates for measurement error.

Results: We observed elevated risks of incident lung cancer with exposures to BS (HR=1.16, 95% CI: 1.02, 1.32, per 10 µg/m³), NO₂ (HR=1.29, 95% CI: 1.08, 1.54, per 30 µg/m³), PM_{2.5} (HR=1.17, 95% CI: 0.93, 1.47, per 10 µg/m³), and with measures of traffic at the baseline address. The exposures were positively associated with all lung cancer subtypes. After adjustment for measurement error, the HRs increased and the 95% CIs widened (HR=1.19 (95% CI: 1.02, 1.39) for BS and HR=1.37 (95% CI: 0.86, 2.17) for PM_{2.5}).

Conclusions: These findings add support to a growing body of literature on the effects of air pollution on lung cancer. In addition, they highlight variation in measurement error by pollutant and support the implementation of measurement error corrections when possible.

Introduction

A growing literature has demonstrated positive associations between long-term exposures to ambient air pollution and an increased risk of lung cancer. The majority of studies have focused on particulate matter; in a recent meta-analysis including 18 studies, each $10 \mu\text{g}/\text{m}^3$ increase in particulate matter less than 2.5 microns in diameter ($\text{PM}_{2.5}$) was associated with a meta-relative risk of 1.09 (95% Confidence Interval (CI): 1.01, 1.14) (Hamra et al. 2014). However, increases in lung cancer risk have also been observed with roadway proximity and exposures to traffic-related pollutants including oxides of nitrogen (NO_2 and NO_x), polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs) (Abbey et al. 1999; Beelen et al. 2008; Carey et al. 2013; Cesaroni et al. 2013; Filleul et al. 2005; Hart et al. 2011; Heinrich et al. 2013; Hystad et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lipsett et al. 2011; Nyberg et al. 2000; Puett et al. 2014; Raaschou-Nielsen et al. 2010; Raaschou-Nielsen et al. 2013; Villeneuve et al. 2013; Villeneuve et al. 2014; Vineis et al. 2006; Yorifuji et al. 2013). Therefore, the International Agency for Research on Cancer (IARC) recently declared ambient air pollution generally, and particulate matter specifically, carcinogenic to humans (Loomis et al. 2013).

Empirical adjustment for bias due to exposure measurement error has been applied in occupational, nutritional, and environmental epidemiology studies (Allodji et al. 2012; Armstrong 2004; Armstrong 1990; Fearn et al. 2008; Heid et al. 2004; Horick et al. 2006; Keshaviah et al. 2003; Li et al. 2006; Rosner et al. 1990; Spiegelman 2010; Van Roosbroeck et al. 2008b; Zhukovsky et al. 2011). Using regression calibration, bias due to exposure measurement can be adjusted for when a validation study is available which contains information

on both the standard exposure collected for the participants in the main study, as well as the “gold standard” exposure collected only in the validation study. To date, however, no study of the chronic effects of air pollution on the risk of lung cancer has incorporated adjustment for exposure measurement error.

We previously examined the associations of long-term exposures to traffic-related exposures and the risk of incident lung cancer from the Netherlands Cohort Study on Diet and Cancer (NLCS) and observed no elevations with specific pollutants, but small elevations in risk with measures of roadway proximity and traffic density (Beelen et al. 2008). Our current objective is to extend these analyses with an additional 7 years of follow-up, to determine the association of air pollution with specific histological subtypes, and to perform analyses incorporating adjustment for measurement error, using information from an exposure validation study (Van Roosbroeck et al. 2008a).

Methods

Study population

Details of the NLCS population have been reported previously (Beelen et al. 2008; van den Brandt et al. 1990). Briefly, the cohort was initiated in September 1986 with 120,852 subjects aged 55 to 69 years of age living in 204 municipalities throughout the Netherlands who had not previously had cancer (other than skin cancer). All participants provided detailed information on diet, lifestyle factors, and personal characteristics at baseline. The study was designed as a case-cohort study, where cases arise over follow-up from the full cohort, but the characteristics of person-years at risk were estimated from a randomly selected subcohort of 5,000 participants. We excluded any participants from the current analysis with missing data on the exposures of

interest, or on current cigarette, pipe, or cigar smoking status, resulting in a final subcohort of 4,666 members. The study was approved by the Maastricht University and the Netherlands Organization for Applied Scientific Research Institutional Review Boards and the Human Subjects Committee of the Harvard T.H. Chan School of Public Health. All cohort members consented to participate in the study by completing and returning the self-administered questionnaire.

Outcome assessment

Participants were followed through December 31, 2003, for a total of 17.3 years of follow-up. Incident cases of the first occurrence of primary lung cancer (International Classification of Diseases for Oncology (ICD-O-3) code C34) were identified by linkage of the full cohort to the Netherlands Cancer Registry and to the nationwide network and registry of histopathology and cytopathology (PALGA). A total of 3,355 incident cases of lung cancer (1,298 squamous cell (ICD-O-3 8050-8076), 573 small cell carcinomas (ICD-O-3 8040-8045), 498 large-cell carcinomas (ICD-O-3 8012-8031, 8310), 737 adenocarcinomas (ICD-O-3 8140, 8211, 8230-8231, 8250-8260, 8323, 8480-8490), and 249 with other or unknown histological subtypes) were identified.

Exposure assessment

Each exposure metric was calculated based on only the baseline (1986) home address of each participant. The methods for calculating long-term average (1987-1996) exposures NO₂, black smoke (BS), and PM_{2.5} have been described in detail (Beelen et al. 2007; Beelen et al. 2008). In brief, the regional, urban, and local contributions of each pollutant were determined and summed to obtain background concentrations (the sum of regional and urban contributions), or overall

concentrations (the sum of the background and local contributions) for each participant. The regional contribution was predicted using inverse distance weighting of monitoring at regional background locations from the National Air Quality Monitoring Network, while urban predictions were estimated using a land-use regression model including data from all regional and urban background monitoring sites and variables for population density and residential or industrial land use. The local contribution was estimated from land use regressions incorporating monitoring data from field monitoring campaigns and a variety of traffic variables as predictors. Three measures of exposure to traffic were defined using a Geographic Information System (GIS) using a digital road network and traffic intensity information from 1986; (1) an indicator for living near a major road, defined as within 100m of a motorway or within 50m of a local road with $\geq 10,000$ vehicles per 24 hours; (2) the traffic intensity in vehicles per 24 hours on the nearest road; and (3) the sum of traffic intensity times road length within a 100m buffer around the residential address in vehicles per 24 hours. We have previously shown that although the traffic intensities have increased during the follow-up period, data from different years were highly correlated, even over periods as long as 10 years (Beelen et al. 2007; Beelen et al. 2008).

Exposure validation data

Details of the validation study have also been published previously (Van Roosbroeck et al. 2008a). Briefly, personal and near-home outdoor exposures to $PM_{2.5}$ absorbance, NO_2 , and $PM_{2.5}$ were collected for 48 hours up to five times from 47 adult nonsmoking participants living in Utrecht between November 2004 and July 2005. $PM_{2.5}$ absorbance and BS are both surrogates of black carbon obtained by filter reflectance measurement but from different types of filters (Roorda-Knape et al. 1998). Approximately 50% lived near roads with a traffic intensity $\geq 10,000$ vehicles/24 hours and 50% on streets with less than 5,000 vehicles/24 hours, more than

50m from a road \geq 10,000 vehicles/24 hours, and more than 400m away from freeways with traffic intensities higher than 70,000 vehicles/24 hours. We explored the utility of this validation study to correct our health effect estimates for the difference between personal and ambient measures of BS, NO₂, and PM_{2.5}.

Statistical analysis

Cox proportional hazards models were used to determine the associations of each measure of exposure to traffic or air pollution with risk of incident lung cancer overall or specific histological subtype. For continuous exposures, after assessing linearity using restricted cubic splines (Durrleman and Simon 1989; Govindarajulu et al. 2007), and performing log-likelihood tests to determine the best-fitting model, we calculated hazard ratios (HRs) and 95% CIs for an interquartile range increase (10 $\mu\text{g}/\text{m}^3$ for BS and PM_{2.5}, 30 $\mu\text{g}/\text{m}^3$ for NO₂, 10,000mvh/24 hours for traffic intensity on the nearest road, and 335,000 mvh/24 hours for traffic intensity in a 100m buffer). To account for the additional variance introduced by the case-cohort design, standard errors were estimated using the robust sandwich estimator (Lin and Wei 1989). We adjusted for a number of *a priori* potential confounders including: age (as the time metric), sex, body mass index, cigarette, cigar, and pipe smoking status, number of cigarettes/cigars/pipes smoked on average, years of each type of tobacco use, home exposure to secondhand smoke, educational attainment, classification of the last occupation, and consumption of alcohol, fruits, vegetables, and fish and shellfish. We also adjusted all models for area-level indicators of socioeconomic status (SES) based on data from Statistics Netherlands: % of individuals below the 40th percentile and % of individuals above the 80th percentile of the Dutch income distribution were calculated at both the neighborhood and “COROP area scale”. The COROP areas were defined in 1970 by the Dutch Coordination Commission for Regional Research Program to be a

geographic region consisting of a city and the surrounding economic and social region. Missing indicator variables were created as needed for all variables. In sensitivity analyses, each *a priori* confounder (or group of confounders) was added to our basic models to determine if it (they) changed the association of any exposure on the risk of overall lung cancer by 10% (Greenland 1989). These confounders were then included in an alternate multivariable model to determine the sensitivity of our findings to our *a priori* selections. In sensitivity analyses to adjust our variance estimates for potential non-independence among participants living in similar areas, we included random effects for each of the COROP areas in our multivariable models.

We performed stratified analyses by cigarette smoking status (current, former, never), overall tobacco use (current, former, never), and sex and created multiplicative interaction terms to assess effect modification. We also used multiplicative interaction terms to test effect modification by study follow-up period (original vs. extended). To test for heterogeneity in effect estimates across lung cancer subtypes we used partial likelihood ratio tests from polytomous regressions using the publically available [SUBTYPE](#) macro (Kuchiba et al. 2014). A p-value of 0.05 was used to denote statistical significance.

Measurement error adjustment

We used the regression calibration method to adjust for bias due to exposure measurement error (Rosner et al. 1990; Spiegelman et al. 1997), using the publically available [BLINPLUS](#) macro (Logan and Spiegelman 2012). First, we obtained the basic and multivariable adjusted HRs and 95% CIs as described above. Next, in the validation study, we regressed the measures of personal exposure on ambient exposure, while controlling for age and sex. Then, measurement error corrected point and interval estimates of the HRs were calculated by combining the

uncorrected HRs from the Cox model with the validation study exposure regressions using a multivariate version of the following equation: $\hat{\beta}_1 = \hat{\beta}_1^*/\hat{\gamma}_1$, where $\hat{\beta}_1$ is the measurement error corrected effect estimate, $\hat{\beta}_1^*$ is the uncorrected effect estimate, and $\hat{\gamma}_1$ is the slope of the regression of personal exposure on exposure surrogate estimated in the validation study. The variance for the measurement error corrected estimates incorporates the variance from estimating β_1^* in the main study, as well as from estimating γ_1 in the validation study using the multivariate delta method.

As shown in previous simulation studies (Kuha 1994; Rosner et al. 1989; Rosner et al. 1990; Spiegelman et al. 1997; Spiegelman et al. 2001), regression calibration can be reliably performed when a number of assumptions have been satisfied. The assumptions include (1) the relationship between the personal and ambient exposure must be linear and homoscedastic; (2) the associations between outcome and exposure must be linear on the scale of the link function used; (3) the degree of measurement error is not severe; (4) non-differential measurement error; and (5) the ambient exposure measure would not be associated with the outcome of interest if personal exposures were available. We examined the validity of the linearity assumptions using restricted cubic regression splines. Homoscedasticity in the validation study model was assessed by calculating the correlation between the predicted values and the absolute residuals from the linear regression models, and the statistical significance of deviations was assessed with the White test (White 1980). The magnitude of measurement error was examined by calculating $\hat{\beta}_1^2 \hat{\sigma}^2$, where $\hat{\sigma}^2$ is the residual variance from the regression of the personal exposures on the ambient exposures. Simulation studies have found that measurement error corrections are accurate when $\beta_1^2 \sigma^2 < 0.5$ (Kuha 1994). Non-differential measurement error is reasonably

assumed in this setting, where the exposure is measured prospectively and objectively, and participants subsequently followed for the occurrence of lung cancer. The fifth assumption is assumed to hold, as there is no reason to assume that ambient exposures would be associated with lung cancer independently of associations with personal exposures. In addition to the above assumptions, we must make the empirically unverifiable transportability assumption that the slope of the regression of the personal exposure on the ambient exposures found in the validation study would be similar to the one which would be found in the main study population. All data analyses were performed in SAS 9.3.

Results

Cases were more likely to smoke cigarettes, cigars, and pipes than subcohort members, and were more exposed to secondhand smoke from a spouse (Table 1). They were also more likely to be male, to be less educated, and to work in blue-collar occupations. There was little difference in the measures of exposure and area-level SES between the cases and subcohort members, and the distributions of BMI and age were similar.

In age- and sex-adjusted models, HRs for all three pollutants and the measures of traffic exposure were above the null for associations with all lung cancer cases and with the specific histological subtypes (Table 2). There was no statistically significant evidence of heterogeneity across subtypes (all *p*-for-heterogeneity > 0.19). In models adjusted for our full set of *a priori* confounders, the HRs generally remained positive. All forms of tobacco use, educational attainment, marital status, occupation, diet, alcohol consumption, and neighborhood- and COROP-level SES were included in the parsimonious multivariable models, and results were similar to those from the *a priori* multivariable models (see Supplemental Material, Table S1).

Although the random term for COROP area was statistically significant for many models (data not shown), the HRs from models accounting for potential clustering were similar to our main models (see Supplemental Material, Table S1). There was no evidence of effect modification by cigarette smoking status, other tobacco use, sex, or follow-up period (p-values for interaction > 0.05; data not shown).

There was no evidence of deviations from linearity or evidence of deviations from homoscedasticity for any of the examined exposures in the validation data (Table 3, calculated with data from (Van Roosbroeck et al. 2008a)). Based on $\beta_1^2 \sigma^2$, the magnitude of measurement error was well within the bounds of the Kuha criterion ($\beta_1^2 \sigma^2 < 0.5$ (Kuha 1994)) for validity of regression calibration for BS ($\beta_1^2 \sigma^2$ s of 0.008, 0.007, 0.011, 0.010, and 0.007, for all cases, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinomas, respectively), and for PM_{2.5} ($\beta_1^2 \sigma^2$ s of 0.316, 0.279, 0.224, 0.634, and 0.224, for all cases, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinomas, respectively). However, the Kuha criterion was not satisfied for NO₂ ($\beta_1^2 \sigma^2$ s 2.052, 1.753, 2.523, 2.281, and 2.033, for all cases, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinomas, respectively). Therefore, any error corrections for NO₂ would not be appropriate.

After adjustment for measurement error, the HRs for BS and PM_{2.5} were further from the null than the HRs before adjustment, with increases from 0-3.3% for BS and 9.7-37.2% for PM_{2.5} (Table 4). The magnitude of the percent increase in the width of the confidence intervals was generally an order of magnitude larger, with increases of 10.2-23.3% for BS and 108.0-216.8% for PM_{2.5}.

Discussion

In this extended follow-up of the NLCS, HRs were above the null for risks of overall and histologic-subtype specific lung cancer for exposures to BS, NO₂, PM_{2.5}, and with measures of traffic at the baseline address, even after adjustment for a number of lifestyle and dietary factors, personal and area-level socioeconomic status. Associations were positive for all histologic subtypes, however, there was no statistically significant heterogeneity observed. Adjustment for measurement error to account for the differences between personal and ambient exposures led to modest increases in the HRs for BS (0-3.3%) and moderate increases in the HRs for PM_{2.5}, (9.7-37.2%), along with substantial widening of the confidence intervals (10.2-216.8%).

Adjustment for various aspects of measurement error has become more common in studies of air pollution in recent years. Several methods have been proposed to address the impact of potential errors induced due to the spatial modeling of exposure (Molitor et al. 2007; Sheppard et al. 2012; Szpiro et al. 2011; Szpiro and Paciorek 2013). Others have adjusted estimates of the effects of air pollution on some health endpoints for the differences between personal and ambient point exposures (Avery et al. 2010a, b; Holliday et al. 2014). These authors used random-effects meta-analysis of literature-based reported correlations between personal and ambient exposures to impute personal exposures for the main study.

Although there was little evidence of effect modification by follow-up period, our results had HRs of greater magnitude and more were statistically significant compared to our previous findings in this cohort (Beelen et al. 2008). For example, in the current analysis, the HR for BS was 1.16 (95%CI: 1.02, 1.32, per 10 µg/m³), compared to an equivalent HR of 1.03 (95%CI: 0.78, 1.34) in our previous analysis. Additionally, we observed HRs above 1 with exposures to

PM_{2.5} and NO₂, which were not observed in the previous analysis. However, although we had previously observed differences in these associations by smoking status, we did not observe statistically significant differences by smoking status in the current analysis.

Most studies of PM_{2.5} on lung cancer risk have reported positive associations, even with a wide variety of approaches to exposure assessment, and a mix of incident and mortality studies (Cao et al. 2011; Carey et al. 2013; Cesaroni et al. 2013; Hart et al. 2011; Hystad et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lepeule et al. 2012; Lipsett et al. 2011; McDonnell et al. 2000; Puett et al. 2014; Raaschou-Nielsen et al. 2013). Our measurement error corrected and uncorrected HRs for PM_{2.5} on overall lung cancer incidence are near the higher end of the distribution of results from previous studies (see Supplemental Material, Table S2). In a recent meta-analysis that included the estimate from our previous NLCS lung cancer analysis, the RR for a 10 µg/m³ increase was estimated to be 1.09 (95%CI; 1.04, 1.14)(Hamra et al. 2014).

A large number of studies from around the world have also reported that NO₂ exposures are positively associated with lung cancer risk (Abbey et al. 1999; Carey et al. 2013; Cesaroni et al. 2013; Filleul et al. 2005; Hart et al. 2011; Heinrich et al. 2013; Hystad et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lipsett et al. 2011; Nyberg et al. 2000; Raaschou-Nielsen et al. 2013; Villeneuve et al. 2014; Yorifuji et al. 2013). Our HR of 1.29 (95%CI: 1.08, 1.54 for each 30 µg/m³ increase in NO₂) is near the center of the distribution of findings from previous studies (see Supplemental Material, Table S3). As with PM_{2.5}, positive associations have been reported based on a wide variety of study types from around the world, with a number of different approaches to exposure assessment.

To our knowledge, only two other population-based studies have explored the associations of BS or related measures with risk of lung cancer. In the French Pollution Atmospherique et Affections Respiratoires Chronique (PAARC) study, exposure to BS in seven French cities was associated with an increased risk of lung cancer (adjusted HR=1.03, 95%CI:0.92, 1.15 for each $10 \mu\text{g}/\text{m}^3$ increase) (Filleul et al. 2005). The multi-country European Study of Cohorts for Air Pollution Effects (ESCAPE) study used $\text{PM}_{2.5}$ absorbance as a marker of BS, and also observed positive associations (HR=1.12, 95%CI: 0.88, 1.42, per $10^{-5}/\text{m}$ increase) (Raaschou-Nielsen et al. 2013).

Results of studies examining the impact of roadway proximity on the risk of lung cancer risk have been more mixed. In addition to our previous analysis, a number of other studies have examined distance to roadway or traffic intensity as an exposure (Cesaroni et al. 2013; Hystad et al. 2013; Puett et al. 2014; Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Vineis et al. 2006). Similar to our findings, these studies have generally observed modest increases in lung cancer risk. Given the heterogeneity in methods and definitions; however, the different metrics are difficult to compare and few studies have observed statistically significant results.

Although we observed HRs of different magnitudes for the different lung cancer subtypes we examined, there was no statistically significant heterogeneity between the subtypes. Differences of effect between subtypes are of great interest, but to date only a limited number of studies have examined histological subtype-specific effects. This interest in differences by subtype is motivated by differences in risk observed with exposures to cigarette smoking. For example, small cell carcinoma, squamous cell carcinoma, and adenocarcinomas have been the subtypes most closely associated with cigarette smoking (Boyle et al. 2010; Tse et al. 2009). Stronger

associations with various pollutants have been observed for adenocarcinomas and squamous cell carcinomas. Specifically, in ESCAPE, elevated HRs were observed in models of PM_{2.5} exposure restricted to these two subtypes when compared to models of all cases (Raaschou-Nielsen et al. 2013). In a case-control study in Canada, subtype specific results for PM_{2.5} and NO₂ were mixed, with a suggestion of a larger risk for adenocarcinomas compared to other subtypes (Hystad et al. 2013). Positive associations with exposures to PM were also observed for adenocarcinomas compared to all lung cancer cases in a study of US nurses (Puett et al. 2014).

This study has several limitations. We used exposures based on the baseline home address as a proxy for actual exposures over time. However, a number of studies have also demonstrated that land-use regressions, such as the one used here, are quite robust to historical changes (Cesaroni et al. 2012; Eeftens et al. 2011; Gulliver et al. 2013). Our inability to incorporate changes in residence during the study period would have induced further exposure misclassification. Another limitation is that we were not able to adjust our analyses of NO₂ (due to violations in the required assumptions) and the traffic proximity and volume measures (due to a lack of data in the validation study) for measurement error. The high $\beta_1^2\sigma^2$ for NO₂ is likely due to the presence of indoor sources or low air exchange rates, which have been consistently observed in other studies (Kousa et al. 2001; Lai et al. 2004; Rotko et al. 2001; Sahuvaroglu et al. 2009; Zipprich et al. 2002). Given the differences measurement error for PM_{2.5} and BS, it is not possible to determine the potential magnitude error that would be observed for NO₂. We are also not able to quantify the impact of indoor sources of NO₂ on lung cancer risk. Therefore, our NO₂ associations should be treated with caution and only interpreted as the ambient effects of these exposures. Lastly, as with all studies, residual confounding is a concern. Our study was not able to update potential confounders, such as smoking or diet, after baseline, and we were missing information on

potential confounders such as secondhand smoke and occupation for around 10% of the study participants.

Our validation study and measurement error approach also have some limitations. Information was only available from 45 individuals, with a little over 200 individual sampling sessions. This limits our ability to examine personal characteristics that may impact the personal and ambient exposure relationships. We were not able to directly measure BS in the validation study, and instead measured PM_{2.5} absorbance, which is measured from another type of filter. However, these two measurements are highly correlated ($R^2=0.94$) (Roorda-Knape et al. 1998), so this is unlikely to be a major source of error. There were also a number of differences between the population measured in the validation study and the individuals in the subcohort. For example, the validation study was composed of nonsmokers in a single metropolitan area of the Netherlands, and it was conducted after the NLCS follow-up. If there are substantially different relationships of personal to ambient exposure measures between the members of the validation study and NLCS, then the assumption of transportability would be violated, and it would not be appropriate to measurement error correct. The personal concentrations are affected by both indoor and outdoor sources. For studies on outdoor air pollution, it has been argued that personal exposure to outdoor and indoor generated particles should be considered separately (Wilson et al. 2000; Wilson and Brauer 2006). The correlation between outdoor exposure and the personal exposure to ambient origin pollution is the most relevant correlation, but difficult to assess. One method is to exclude the main indoor source from the study, as was done in the current validation study by excluding smokers.

This study also has major strengths. The long follow-up period and high rate of case ascertainment have provided us with a large number of cases with information on histological subtype. This allows us to examine the impact of a number of pollutants on subtype-specific risks, which to date has only been possible in a handful of studies. Our use of regression calibration to adjust for bias due to measurement error in predicted ambient pollutant concentrations in relation to personal exposure measurements, while imperfect, provides a sense of the level of underestimation in studies that are unable to perform this correction for measurement error bias.

In conclusion, in this large study based in the Netherlands, we observed an elevated risk of overall and histologic subtype specific incident lung cancer with long-term exposure to BS, NO₂, PM_{2.5}, and with measures of traffic at the baseline address. The HRs increased after correction for measurement error, although the impact of the adjustment for measurement error varied between the two pollutants where adjustment was possible. Correction for measurement error also resulted in substantial losses in precision. These findings add support to a growing body of literature on the effects of air pollution on lung cancer, as well as to the recent classification of air pollution as a human carcinogen by IARC (Loomis et al. 2013).

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Table 1. Baseline (1986) characteristics of the lung cancer cases and the subcohort from the Netherlands Cohort Study on Diet and Cancer (N=7,881).

Characteristic	Cases (N=3,355)	Subcohort (N=4,666)
Median (IQR)		
Age (years)	62 (7)	61 (7)
Fruit and fruit preserves consumed (g/day)	106 (146)	145 (150)
Vegetables consumed (g/day)	165 (102)	175 (102)
Fish and shellfish consumed (g/day)	8 (20)	7 (20)
% neighborhood below 40 th percentile of income	41 (11)	40 (10)
% neighborhood above 80 th percentile of income	17 (12)	18 (13)
% COROP area below 40 th percentile of income	41 (9)	41 (9)
% COROP area above 80 th percentile of income	19 (5)	19 (5)
Average Black Smoke 1987-1996 ($\mu\text{g}/\text{m}^3$)	16.7 (4.0)	16.6 (4.0)
Average NO ₂ 1987-1996 ($\mu\text{g}/\text{m}^3$)	38.0 (11.0)	37.8 (11.1)
Average PM _{2.5} 1987-1996 ($\mu\text{g}/\text{m}^3$)	28.3 (2.4)	28.3 (2.5)
%		
Male	85.3	48.9
Marital status		
Married	84.3	78.1
Single, divorced, widowed	15.6	21.5
Missing	0.1	0.4
Cigarette smoking status		
Never	6.8	36.3
Former	29.5	35.1
Current	63.8	28.6
Cigar smoking status		
Never	77.3	87.4
Former	6.6	5.4
Current	15.4	6.5
Pipe smoking status		
Never	87.3	92.5
Former	3.4	3.6
Current	8.2	3.1
Cigarette smoking spouse		
Never	41.3	30.8
Former	17.1	27.8
Current	34.2	31.6
N/A or Missing	7.4	9.9
Alcohol consumption (g/day)		
<0.4 (Abstainer)	14.5	22.2
0.4-4	18.3	27.0
5-14	22.8	21.7
15-29	22.6	15.0
≥ 30	18.2	8.8

Characteristic	Cases (N=3,355)	Subcohort (N=4,666)
Missing	3.6	5.3
Educational Attainment		
Primary/Lower vocational school	24.4	20.3
High school	55.0	51.5
Higher vocational or university	19.9	27.3
Missing	0.8	0.9
Body Mass Index (kg/m²)		
<20	3.7	3.5
20-<25	50.6	48.2
25-<30	38.2	38.3
≥30	4.0	6.4
Missing	3.6	3.6
Last Occupation		
Blue collar	36.7	26.7
Low white collar	12.6	15.8
White collar	20.7	19.8
Other	14.7	15.5
Last occupation ≥ 40 years ago	1.6	5.0
Never paid employment	1.4	6.5
Missing	12.4	10.7

Table 2. Associations of Increases in Average Black Smoke, NO₂, or PM_{2.5} Exposures 1987-1996 or Baseline Address Traffic Measures with Incident Lung Cancer 1986-2003 Overall and by Subtype.

Exposure	All Lung Cancer HR (95%CI)	Squamous Cell Carcinoma HR (95%CI)	Small Cell Carcinoma HR (95%CI)	Large Cell Carcinoma HR (95%CI)	Adenocarcinoma HR (95%CI)
Number of cases	3,355	1,298	573	498	737
Black smoke (10 µg/m ³)					
Basic model ^a	1.23 (1.08, 1.40)	1.16 (0.96, 1.40)	1.24 (0.96, 1.60)	1.22 (0.94, 1.59)	1.42 (1.14, 1.78)
Multivariable model ^b	1.16 (1.02, 1.32)	1.14 (0.94, 1.38)	1.24 (0.95, 1.61)	1.22 (0.91, 1.62)	1.14 (0.90, 1.44)
NO ₂ (30 µg/m ³)					
Basic model ^a	1.24 (1.05, 1.47)	1.09 (0.86, 1.38)	1.21 (0.87, 1.69)	1.26 (0.89, 1.78)	1.65 (1.24, 2.21)
Multivariable model ^b	1.29 (1.08, 1.54)	1.24 (0.96, 1.61)	1.37 (0.95, 1.97)	1.33 (0.90, 1.97)	1.29 (0.93, 1.78)
PM _{2.5} (10 µg/m ³)					
Basic model ^a	1.12 (0.89, 1.40)	1.02 (0.73, 1.41)	1.11 (0.71, 1.72)	1.17 (0.73, 1.87)	1.44 (0.98, 2.11)
Multivariable model ^b	1.17 (0.93, 1.47)	1.15 (0.82, 1.61)	1.12 (0.71, 1.77)	1.37 (0.83, 2.26)	1.12 (0.74, 1.70)
Living near a major road					
Basic model ^a	1.18 (0.96, 1.45)	1.15 (0.87, 1.54)	1.39 (0.96, 2.00)	1.28 (0.86, 1.91)	1.15 (0.81, 1.63)
Multivariable model ^c	1.12 (0.92, 1.37)	1.08 (0.80, 1.44)	1.40 (0.96, 2.02)	1.25 (0.83, 1.88)	1.05 (0.75, 1.47)
Traffic intensity on the nearest road (10,000 mvh/24h)					
Basic model ^a	1.06 (0.96, 1.17)	1.07 (0.95, 1.21)	1.08 (0.89, 1.32)	1.03 (0.86, 1.23)	1.05 (0.92, 1.20)
Multivariable model ^c	1.02 (0.93, 1.12)	1.03 (0.91, 1.15)	1.06 (0.87, 1.29)	1.01 (0.84, 1.21)	0.99 (0.86, 1.14)
Traffic intensity in a 100-m buffer (335,000 mvh/24 h)					
Basic model ^a	1.15 (1.01, 1.31)	1.21 (1.01, 1.44)	1.13 (0.87, 1.46)	1.03 (0.79, 1.35)	1.20 (0.97, 1.49)
Multivariable model ^c	1.10 (0.97, 1.24)	1.17 (0.98, 1.39)	1.15 (0.89, 1.47)	0.98 (0.75, 1.29)	1.10 (0.89, 1.36)

^aAdjusted for age and sex. ^bAdditionally adjusted for cigarette, cigar, and pipe smoking status, years and amount of cigarette, cigar, and pipe smoking, secondhand smoke exposure, marital status, educational status, occupational status, marital status, BMI, alcohol consumption, intake of fruits, vegetables, and fish, and neighborhood- and COROP-level SES. ^cAdjusted for all covariates in the default multivariable model plus regional and urban background black smoke.

Table 3. Exposure Information from the Validation Study (Van Roosbroeck et al. 2008a)
Available for Measurement Error Correction.

Data	PM_{2.5} absorbance* (10⁻⁵m⁻¹)	NO₂ (µg/m³)	PM_{2.5} (µg/m³)
N	172	209	174
Measured Personal Exposure, Mean ± SD	1.71 ± 0.70	26.9 ± 11.3	16.8 ± 11.2
Measured Ambient Exposure, Mean ± SD	1.61 ± 0.63	32.0 ± 8.4	18.2 ± 10.0
Ratio of Personal and Ambient SDs	1.11	1.35	1.12
Correlation of Personal and Ambient Exposures	0.78	0.04	0.45
Validation model R ²	0.62	0.22	0.21
P-value for Test of Heteroscedasticity	0.74	0.14	0.77
σ ²	0.044	0.326	1.004
Deattenuation factor ^a	0.87	0.05	0.50

*PM_{2.5} absorbance was measured in the validation study and is used to adjust models for black smoke.

^aThe deattenuation factor is calculated by multiplying the ratio of the personal and ambient exposure standard deviations by the correlation between the personal and ambient measures.

Table 4. Measurement Error Adjusted Associations per Interquartile Range Increase in Black Smoke or PM_{2.5} Exposures on the Risk of Incident Lung Cancer 1986-2003 Overall and by Subtype.

Exposure	All Cases HR (95% CI) ^a	Squamous Cell Carcinoma HR (95% CI) ^a	Small Cell Carcinoma HR (95% CI) ^a	Large Cell Carcinoma HR (95% CI) ^a	Adenocarcinomas HR (95% CI) ^a
Black smoke (10 µg/m ³)	1.19 (1.02, 1.39)	1.17 (0.93, 1.47)	1.28 (0.94, 1.75)	1.26 (0.90, 1.76)	1.17 (0.89, 1.54)
% increase in HR ^b	2.6	2.6	3.2	3.3	0.0
% increase in 95% CIs ^c	23.3	22.7	22.7	21.1	10.2
PM _{2.5} (10 µg/m ³)	1.37 (0.86, 2.17)	1.32 (0.67, 2.61)	1.25 (0.50, 3.15)	1.88 (0.68, 5.21)	1.25 (0.54, 2.89)
% increase in HR ^b	17.1	14.8	11.6	37.2	9.7
% increase in 95% CIs ^c	142.6	145.6	150.0	216.8	108.0

^aMultivariable model adjusted for age and sex, cigarette, cigar, and pipe smoking status, years and amount of cigarette, cigar, and pipe smoking, secondhand smoke exposure, educational status, occupational status, marital status, BMI, alcohol consumption intake of fruits, vegetables, and fish, and neighborhood- and COROP-level SES. ^b $[(HR_{\text{multivariable}} - HR_{\text{measurement error}})/HR_{\text{multivariable}}]*100$. ^c $[(UCL_{\text{multivariable}} - LCL_{\text{multivariable}}) - (UCL_{\text{measurement error}} - LCL_{\text{measurement error}})] / (UCL_{\text{multivariable}} - LCL_{\text{multivariable}})]*100$.