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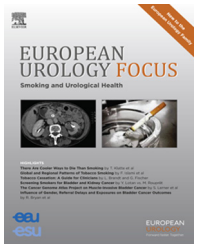

Epidemiology

Is There an Association Between Ambient Air Pollution and Bladder Cancer Incidence? Analysis of 15 European Cohorts

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Abstract

Background: Ambient air pollution contains low concentrations of carcinogens implicated in the etiology of urinary bladder cancer (BC). Little is known about whether exposure to air pollution influences BC in the general population.
Objective: To evaluate the association between long-term exposure to ambient air pollution and BC incidence.
Design, setting, and participants: We obtained data from 15 population-based cohorts enrolled between 1985 and 2005 in eight European countries ($N = 303\,431$; mean follow-up 14.1 yr). We estimated exposure to nitrogen oxides (NO_2 and NO_x), particulate matter (PM) with diameter <10 μm (PM_{10}), <2.5 μm ($PM_{2.5}$), between 2.5 and 10 μm ($PM_{2.5-10}$), $PM_{2.5\ absorbance}$ (soot), elemental constituents of PM, organic carbon, and traffic density at baseline home addresses using standardized land-use regression models from the European Study of Cohorts for Air Pollution Effects project.
Outcome measurements and statistical analysis: We used Cox proportional-hazards models with adjustment for potential confounders for cohort-specific analyses and meta-analyses to estimate summary hazard ratios (HRs) for BC incidence.
Results and limitations: During follow-up, 943 incident BC cases were diagnosed. In the meta-analysis, none of the exposures were associated with BC risk. The summary HRs associated with a 10-$\mu g/m^3$ increase in NO_2 and 5-$\mu g/m^3$ increase in $PM_{2.5}$ were 0.98 (95% confidence interval [CI] 0.89–1.08) and 0.86 (95% CI 0.63–1.18), respectively. Limitations include the lack of information about lifetime exposure.
Conclusions: There was no evidence of an association between exposure to outdoor air pollution levels at place of residence and risk of BC.
Patient summary: We assessed the link between outdoor air pollution at place of residence and bladder cancer using the largest study population to date and extensive assessment of exposure and comprehensive data on personal risk factors such as smoking. We found no association between the levels of outdoor air pollution at place of residence and bladder cancer risk.

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1. Introduction

Urinary bladder cancer (BC) is the ninth most common cancer worldwide [1]. Smoking is the primary risk factor for BC, with relative risks of three for current smokers and two for former smokers compared to individuals who never smoked [2]. Findings from the most recent studies suggest that the relative risk for current smokers has increased to four or five times the risk for nonsmokers [3]. The relative risk for BC increases with smoking duration and intensity [4]. BC occurs mainly in older people, is more frequent in men, and exhibits large geographical variation [5].

Ambient air pollution includes a mix of carcinogens such as polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds, transition metals, and diesel engine exhaust [6,7]. Ambient air pollution and particulate matter (PM) in ambient air have recently been classified as carcinogenic to humans [6]. This classification was largely based on higher risk of lung cancer [8–10]. However, there is suggestive evidence of an association between ambient air pollution and BC in humans [6,10].

Higher BC risk has been reported in some studies on taxi, bus, and/or truck drivers exposed to high levels of urban air pollution [6], including PAHs [11] and diesel engine exhaust [7], but no risk elevation was found for miners with high diesel exposure [12]. Some of these studies were incidence-based, while others were based on mortality, which may also have contributed to the heterogeneity observed for results. A few studies have investigated a possible association between exposure to ambient air pollution and BC in the general population, and provided mixed results [13–17]. Limitations related to design, poor exposure assessment, and lack of information on potential confounding complicate interpretation of these previous studies.

Our aim was to examine the associations between exposure to ambient air pollution at the place of residence and BC incidence in a large European study population with fine-scale exposure assessment and extensive control for potential confounders such as smoking. We used the same study population, exposure assessment, and data analysis methods as in our previous study documenting significant associations between air pollution and lung cancer [9]

2. Materials and methods

2.1. Study population

The European Study of Cohorts for Air Pollution Effects (ESCAPE) project included 36 European areas where air pollution measurements were performed, exposure models were developed, and cohort studies located [9,18]. The present study included 15 population-based prospective

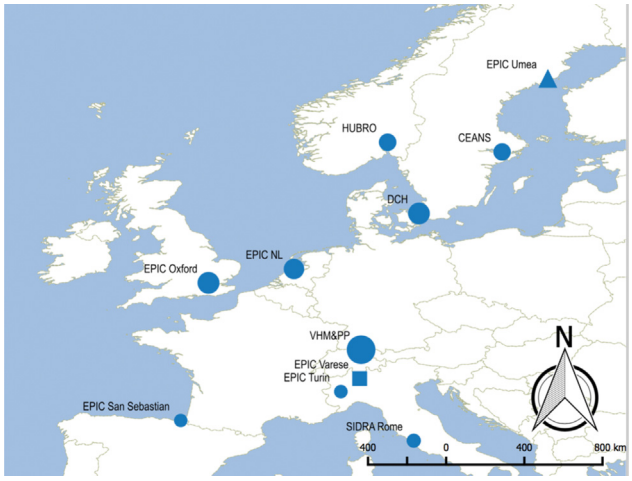

Fig. 1 – Study areas. Circles indicate that NO_2, NO_x, and particulate matter data are available. Triangles indicate that only NO_2, NO_x, and traffic density data are available. The square indicates that only NO_2 and NO_x data are available. The size of the symbol indicates the size of the study cohort (N = 303 431).

cohorts with information on incident BC cases with at least 20 incident BC cases during follow-up and where the resources needed for participation were available. The cohorts were in Sweden (European Prospective Investigation into Cancer and Nutrition[EPIC]-Umea, Swedish National Study on Aging and Care in Kungsholmen [SNAC-K], Stockholm Screening Across the Lifespan Twin Study and TwinGene [SALT], Stockholm 60 years old and IMPROVE study [Sixty], Stockholm Diabetes Prevention Program [SDPP]), Norway (Oslo Health Study [HUBRO]), Denmark (Diet, Cancer and Health Study [DCH]), the Netherlands (EPIC Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [MORGEN], EPIC PROSPECT), the UK (EPIC Oxford), Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]), Italy (EPIC Varese, EPIC Turin, Italian Studies of Respiratory Disorders in Childhood and Environment–Rome [SIDRIA] Rome), and Spain (EPIC San Sebastian). Figure 1 shows the study areas and Supplementary Table 1 lists the population characteristics. A pooled analysis of all cohort data was not possible owing to data-transfer and privacy issues, but data from the four Stockholm cohorts (SNAC-K, SALT, Sixty, and SALT) were pooled, analyzed, and denoted as one cohort (Cardiovascular Effects of Air pollution and Noise in Stockholm [CEANS]). Similarly, data from the two cohorts from the Netherlands (EPIC MORGEN and EPIC PROSPECT) were pooled, analyzed, and denoted as one cohort [EPIC NL] (Supplementary Table 2). Most of the participants were recruited in the 1990s (Table 1). Participants with a cancer (except nonmelanoma skin cancer) before enrolment were excluded, as were participants for whom information about exposure to air pollution and the most important potential confounders could not be obtained. We included 303 431 participants (81.7% of those enrolled).

Each cohort study followed the rules for ethics and data protection in the country in which it was based. All participants gave informed consent.

2.2. Bladder cancer

In all cohorts, follow-up was based on linkage to cancer registries, with the exception of SIDRIA–Rome, for which hospital discharge and mortality register data were used. Cases were defined as participants diagnosed with BC recoded according to ICD-9 code 1880-1889 and ICD-10 code C67. We did not include carcinomas in situ. Only primary cancers (ie, not metastases) and only malignant tumors were included.

2.3. Exposure assessment

Annual average air pollution concentrations at residential addresses at the time of enrolment in the cohort studies were estimated via area-specific land-use regression (LUR) models using standardized methods developed within ESCAPE [19,20].

Air pollution was measured for 1 yr in each study area between October 2008 and May 2011. PM with a diameter of <10 μm (PM_{10}), $PM_{2.5}$, and soot/blackness of the $PM_{2.5}$-exposed filter ($PM_{2.5\ absorbance}$), determined via measurement of light reflectance, were measured at 20 sites. Nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were measured at 40 sites in each of the areas. Sites were selected to represent spatial variations in air pollution in the residential areas. Within each study area, measurements at each site were performed during three 2-wk periods (during summer, winter, and an intermediate season) and the three measurements were averaged, adjusting for temporal trends using continuous data from a reference site [9] to estimate the annual mean at each site. For financial reasons, sampling of PM was not performed everywhere (Fig. 1).

LUR models were then developed for each pollutant in each study area, with the yearly mean concentration as the dependent variable and

Table 1 – Study population characteristics (N = 303 431, n = 943)

Study cohort (country)	Enrolment	N[c]	Persons years at risk	n[d]	Age (yr)[e]	Follow-up (yr)[f]	Men (%)	Smoking (%)[g]
EPIC Umea (Sweden)	1992–1996	21 901	294 493	69	45.9 ± 10.9	13.4 (0.0–16.9)	48	19
HUBRO (Norway)	2000–2001	17 958	152 973	21	47.9 ± 15.2	8.5 (0.0–9.7)	44	26
CEANS (Sweden)[a]	1992–2004	17 534	182 429	60	55.9 ± 11.7	10.4 (0.0–17.8)	37	22
DCH (Denmark)	1993–1997	37 676	556 904	179	56.8 ± 4.3	14.8 (0.0–19.1)	47	37
EPIC NL (The Netherlands)[b]	1993–1997	30 134	355 933	88	50.4 ± 11.3	11.8 (0.0–15.0)	24	29
EPIC Oxford (England)	1993–1998	38 567	423 542	81	45.5 ± 13.7	11.0 (0.0–14.8)	24	11
VHM&PP (Austria)	1985–2005	104 714	1 899 063	306	42.9 ± 14.9	18.1 (0.0–27.0)	44	13
EPIC Varese (Italy)	1993–1997	10 310	111 212	20	51.6 ± 8.2	10.8 (0.0–13.3)	21	21
EPIC Turin (Italy)	1993–1997	7946	104 461	54	50.4 ± 7.5	13.1 (0.0–16.6)	55	24
SIDRIA Rome (Italy)	1999	9105	102 130	38	44.3 ± 6.0	11.2 (0.0–12.0)	47	42
EPIC San Sebastian (Spain)	1992–1995	7586	92 796	27	49.4 ± 7.7	12.2 (0.0–14.7)	46	27

[a] Pooled data from the SNAC-K, SALT, Sixty, and SDPP cohorts.
[b] Pooled data from the EPIC MORGEN and EPIC PROSPECT cohorts.
[c] Total number of participants included.
[d] Number of bladder cancer incidence cases.
[e] Mean ± standard deviation.
[f] Mean (minimum–maximum).
[g] Current smoking.

Table 2 – Exposure distribution by cohort at the baseline addresses

Study cohort	NO_2 ($\mu g/m^3$)	NOx ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	$PM_{2.5\ absorbance}$ ($10^{-5}/m^3$)	PM_{10} ($\mu g/m^3$)	$PM_{2.5-10}$ ($\mu g/m^3$)	Traffic density (vehicles/d)	OC ($\mu g/m^3$)
EPIC Umea	5.2 ± 2.5	8.7 ± 5.8	NA	NA	NA	NA	846 ± 1,532	NA
HUBRO	20.9 ± 8.0	38.3 ± 15.4	8.9 ± 1.3	1.2 ± 0.3	13.5 ± 3.1	4.0 ± 2.0	2501 ± 5,100	NA
CEANS	10.8 ± 4.6	19.0 ± 10.2	7.1 ± 1.3	0.6 ± 0.2	14.6 ± 4.1	7.1 ± 3.2	1556 ± 4,572	NA
DCH	16.4 ± 7.0	26.8 ± 18.4	11.3 ± 0.9	1.2 ± 0.2	17.2 ± 2.0	5.7 ± 1.0	3022 ± 7,249	1.6 ± 0.2
EPIC NL	25.2 ± 6.2	37.9 ± 11.3	16.8 ± 0.6	1.4 ± 0.2	25.4 ± 1.5	8.5 ± 0.9	1291 ± 3,804	1.5 ± 0.4
EPIC Oxford	24.5 ± 8.0	40.9 ± 15.6	9.8 ± 1.1	1.1 ± 0.3	16.1 ± 2.0	6.4 ± 0.9	1383 ± 4,353	NA
VHM&PP	19.9 ± 5.5	39.9 ± 9.5	13.6 ± 1.2	1.7 ± 0.2	20.6 ± 2.4	6.7 ± 0.9	1684 ± 3,584	NA
EPIC Varese	43.5 ± 17.3	86.1 ± 41.8	NA	NA	NA	NA	NA	NA
EPIC Turin	53.2 ± 10.8	96.4 ± 21.0	30.1 ± 1.7	3.1 ± 0.4	46.4 ± 4.2	16.5 ± 2.7	3981 ± 9,272	NA
SIDRIA Rome	39.1 ± 9.1	82.0 ± 23.9	19.4 ± 1.8	2.7 ± 0.5	36.5 ± 5.0	16.7 ± 3.4	2955 ± 6,728	3.5 ± 0.3
EPIC San Sebastian	23.8 ± 6.6	47.2 ± 12.5	NA	NA	NA	NA	NA	NA

OC = organic carbon; NA = not available; NO_x = nitrogen oxides; $PM_{2.5}$ = particulate matter with aerodynamic diameter <2.5 μm; $PM_{2.5-10}$ = coarse PM with aerodynamic diameter 2.5–10 μm; PM_{10} = PM with aerodynamic diameter <10 μm.
Data are presented as the annual mean ± standard deviation.

an extensive list of geographic attributes as possible predictors. Data from the nearest routine monitoring stations were used to back-extrapolate the LUR estimates to the baseline year in 14 of the 15 study areas using the ratio method [21].

We also collected information on traffic intensity (vehicles/d) on the nearest street for all cohorts except for two (Fig. 1, Table 2).

We used the same methods to assess concentrations of eight PM elements [22] and organic carbon in PM [23] to facilitate explorative analyses of associations with BC risk.

2.4. Statistical analysis

Cox proportional hazards models were used for the cohort-specific analyses in accordance with a standardized protocol [9]. Age was used as the time scale. Follow-up started at enrollment in the cohort. Censoring was at the time of death or emigration, a diagnosis of any other cancer (except non-melanoma skin cancer), or the end of follow-up, whichever came first.

Exposure was analyzed as a linear variable. Potential confounders were available from questionnaires at baseline (Supplementary Table 1). We specified a priori three confounder models with increasing levels of adjustment for both individual and contextual socioeconomic status (SES) variables, following the methodology of our previous study on lung cancer [9]. Model 1 included only age (time axis), sex, and calendar time (year of enrollment, continuous). Model 2 added the following individual-level variables (as available for the individual cohorts; all referring to baseline): smoking status (never/former/current), smoking intensity (tobacco g/d, linear and squared term), smoking duration (years), occupational class (ever worked in an industry/job associated with higher BC risk or white/blue collar classification), employment status, and educational level (low, medium, high). Model 3 added area-level SES variables, including mean income, percentage of people with a low income, unemployment rate, and educational level or deprivation index, which were defined for most of the cohorts at the neighborhood or municipality level. Model 3 was selected as the main confounder model. Detailed information on jobs associated with high BC risk was only available for DCH, while three cohorts had less detailed information on occupation and nine cohorts had information on employment status.

We performed the following model checks and sensitivity analyses. First, we tested the linearity assumption in the relation between each exposure and BC by replacing the linear term with a natural cubic spline with two equally spaced inner knots, and compared the model fit of the linear and spline models using a likelihood ratio test. Second, we assessed whether there was a deviation from the proportional hazards assumption in the Cox model. Third, we assessed potential effect modification by sex, smoking status, and level of education. Fourth, we restricted analyses to participants who had lived at the baseline address throughout follow-up to minimize misclassification of long-term exposure relevant to the development of BC. Fifth, we fitted back-extrapolated exposure to take into account long-term trends in air pollution. Finally, we added an indicator of extent of urbanization to the most comprehensively adjusted model.

Cohort-specific effect estimates were combined by random-effects meta-analysis for each exposure when it was available in at least three cohorts [24]. The I^2 statistic and Q test were used to assess heterogeneity among cohort-specific effect estimates [25].

Stata software, version 11 (StataCorp, College Station, TX, USA) was used for all data analyses.

3. Results

3.1. Study population

In total, the 15 cohorts contributed 4,275 936 person-years at risk, and 943 incident BC cases developed during mean follow-up of 14.1 yr (range 0.0–27.0; Table 1). The mean age at baseline was 48 yr, ranging from 43 to 57 yr across cohorts. Some 39% of the participants were men, 21% were current smokers, and 18% were former smokers (Table 1).

The study areas exhibited a wide range of air pollution concentrations between and within each cohort. The modeled mean air pollution concentrations were lowest in the Swedish and highest in the Italian study areas (Table 2, Supplementary Table 3).

3.2. Air pollution, traffic density, and BC

In the meta-analysis, none of the exposures were significantly associated with BC incidence (Table 3, Fig. 2). All exposures investigated, including PM elements (Supplementary Table 4), were associated with HRs close to null. The summary HRs in model 3 associated with a 10-$\mu g/m^3$ increase in NO_2 and 5-$\mu g/m^3$ increase in $PM_{2.5}$ were 0.98 (95% confidence interval [CI] 0.89–1.08) and 0.86 (95% CI 0.63–1.18), respectively.

For all exposures, the summary HRs were essentially HR = 1 in models adjusted for age, sex, and calendar year only. The HRs were slightly reduced in models with comprehensive adjustment (Table 3).

Table 3 – Hazard ratios for the associations between air pollution, traffic density, and bladder cancer

Exposure	Increase	Cohorts	Participants	Cases	Model 1[a]	Model 2[b]	Model 3[c]		
		(*N*)	(*N*)	(*n*)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)[d]	p[d]
NO_2	10 μg/m^3	15	303 431	943	1.01 (0.92–1.11)	0.99 (0.90–1.09)	0.98 (0.89–1.08)	0.0	0.71
NO_x	20 μg/m^3	15	303 431	943	1.03 (0.93–1.13)	1.00 (0.91–1.11)	0.99 (0.91–1.09)	0.0	0.45
$PM_{2.5}$[e]	5 μg/m^3	12	263 634	827	0.96 (0.71–1.31)	0.94 (0.69–1.27)	0.86 (0.63–1.18)	0.0	0.44
$PM_{2.5\ absorbance}$[e]	10^{-5}/m^3	12	263 634	827	0.97 (0.74–1.28)	0.92 (0.70–1.22)	0.87 (0.66–1.16)	0.0	0.50
PM_{10}[e]	10 μg/m^3	12	263 634	827	0.95 (0.62–1.45)	0.93 (0.60–1.43)	0.92 (0.58–1.48)	59.3	0.02
$PM_{2.5-10}$[e]	5 μg/m^3	12	263 634	827	1.15 (0.71–1.84)	1.10 (0.71–1.69)	1.08 (0.70–1.68)	63.7	0.01
Traffic density[f]	5000 vehicles/d	13	285 535	896	0.98 (0.90–1.07)	0.97 (0.90–1.06)	0.98 (0.90–1.06)	7.2	0.38
Organic carbon[g]	1 μg/m^3	3	76 915	305	1.00 (0.54–1.83)	0.91 (0.55–1.53)	0.86 (0.49–1.51)	28.2	0.25

Summary hazard ratio (HR) and 95% confidence interval (CI) from random-effect meta-analysis. No information on occupation or employment is available for the EPIC NL, EPIC Turin, and EPIC San Sebastian cohorts.

[a] Adjusted for age (time scale), sex, and calendar time in the Cox model.

[b] Additional adjustment for smoking (status, intensity, and duration), occupation, employment, and education.

[c] Additional adjusted for area-level SES.

[d] I^2 and p refer to assessment of heterogeneity.

[e] PM data are not available for the EPIC Umea, EPIC Varese, and EPIC San Sebastian cohorts.

[f] Traffic density data are not available for the EPIC Varese and EPIC San Sebastian cohorts.

[g] Organic carbon data are only available for the DCH, EPIC NL, and SIDRIA Rome cohorts.

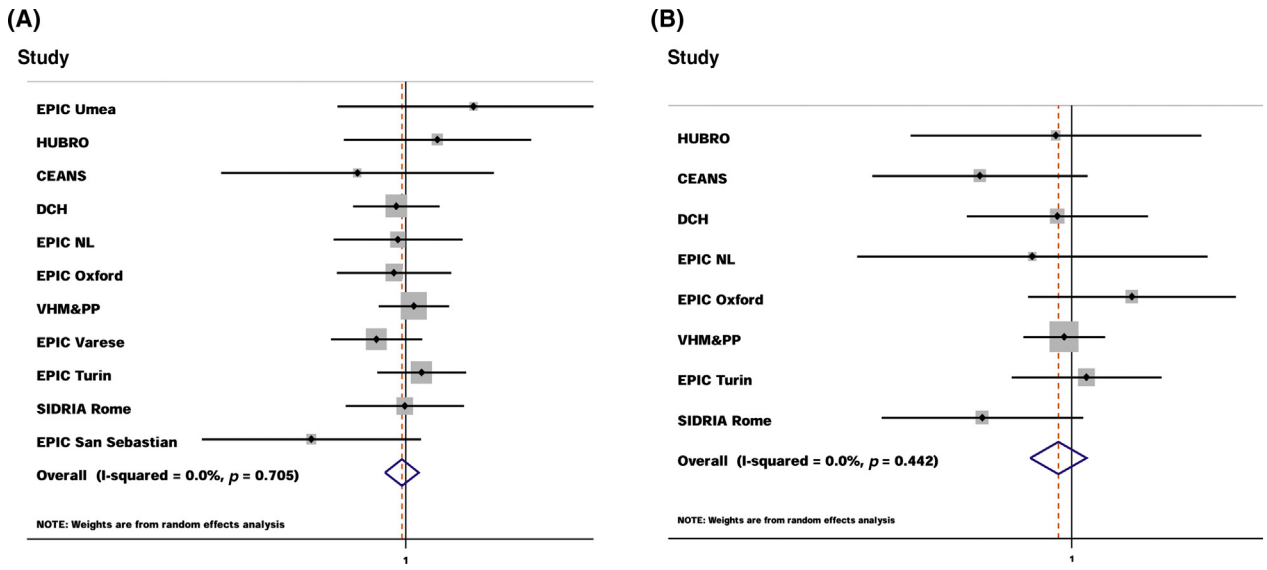

Fig. 2 – Risk of bladder cancer associated with ambient air pollution levels in each cohort study and overall. Hazard ratio (data points) and 95% confidence interval (lines) for bladder cancer (A) per 10 μg/m^3 increment in NO_2 and (B) per 5 μg/m^3 increment in $PM_{2.5}$ from models adjusted for age, sex, calendar time, smoking (status, intensity, and duration), occupation, employment, education, and area-level socioeconomic status. Grey boxes show the weight with which each cohort contributed to the summary hazard ratio. The vertical dashed line shows the summary hazard ratio.

The meta-analyses showed significant heterogeneity between cohorts for PM_{10}, $PM_{2.5-10}$, and a few elemental components of PM, while no substantial heterogeneity was observed for most of the exposures assessed (Table 3, Fig. 2, Supplementary Table 4).

3.3. *Model checks, sensitivity analysis, and effect modification*

In most cohorts, there was no evidence of deviation from linearity for any of the pollutants (Supplementary Tables 5 and 6). All cohorts met the proportional hazards assumptions for Cox models (Supplementary Table 7). Higher risk of BC among men was suggested for NO_2, but the effect modification by sex was borderline statistically significant and not evident for $PM_{2.5}$, and there was no effect modification by smoking habit and education for any of the pollutants (Supplementary Table 8). Results reported in Table 3 were similar to those in a sensitivity analysis restricted to non-movers, models fitted with back-extrapolated exposure to NO_2 and models additionally adjusted for degree of urbanization (Supplementary Table 9).

4. Discussion

In this prospective study of 15 European cohorts, long-term exposure to ambient air pollution was not associated with risk of BC.

Our study is the largest study with detailed individual-level confounder variables to date on the relationship between ambient air pollution and BC in the general population. The lack of an association between air pollution and NO_x, traffic density, PAHs, and BC risk observed in our study is consistent with some previous studies from Denmark, Spain, and the Netherlands [13,14,16] and inconsistent with others from Spain and Taiwan [14,15]. Inconsistency among studies may be partly explained by differences in design, exposure assessment, and ability to adjust for smoking. Only two of the five previous studies adjusted for smoking [13,14]. Three case-control studies reported higher BC risk in association with crude indicators of exposure to outdoor air pollution such as residence in an urban area (22–46% [17], 4–63% [14]) and in municipalities characterized by high air pollution exposure (36–188% [15]). However, residential exposure to specific air pollutants was not assessed at fine-scale individual levels in four of the five previous studies [14–17], the results were not consistent within these studies, and nonsignificant results for other indicators such as residential proximity to PAH emissions or diesel engine exhaust from industries [14] and urban residence [15] were reported too. The previous studies relying on crude area-specific indicators [14,15,17] may have captured differences related to area of living, rather than fine-scale, individual-level differences in air pollution.

Similar to tobacco smoke, it is evident that ambient air pollution can induce DNA damage in the general population [6]. Several studies have linked exposure to ambient air pollution to biomarkers of exposure to genotoxic carcinogens and cancer-related early-effect biomarkers, such as bulky DNA adducts, chromosome aberrations, micronuclei, and DNA methylation [6,26]. Accordingly, carcinogenic genotoxic effects may be induced in the urinary bladder by exposure to ambient air pollution with particles, providing biological plausibility of an association between ambient air pollution and BC.

A major strength of our study is that it relies on 8-yr to 18-yr mean follow-up for large European population-based cohorts spread over a wide geographic area with very different air pollution levels, which adds to the generalizability of the results. Another important strength is the state-of-the-art assessment of quantitative exposure to key air pollutants instead of crude indicators of exposure. We used a standardized extensive exposure assessment that enabled us to assess fine-scale, address-specific, spatial variation in concentrations of a more comprehensive number of air pollutants than in previous studies. In contrast to any prior studies, we were able to assess $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, $PM_{2.5\ absorbance}$, and components of PM. Only a case-control study from Taiwan previously evaluated exposure to PM_{10} [15], but this study relied on routine air pollution monitoring stations, which do not adequately capture within-city exposure variability. Assessment of PM is important because PM is considered to be the most relevant airborne pollutant for carcinogenesis [8,10]. Indeed, our previous analysis showed that higher HRs for lung cancer were associated with long-term exposure to PM, but not NO_2 and NO_x [9]. Furthermore, detailed information about individual baseline characteristics such as smoking habits were available for adjustment. Three of the previous five studies [15–17] could not control for smoking.

Our study has some limitations. The LUR models were developed based on measurements and data from 2008 to 2011, whereas they were applied to baseline home addresses typically 10–15 yr earlier (Table 1). To address this discrepancy, we back-extrapolated exposure to the baseline period using long-term routine monitoring data, which were available for all cohorts except HUBRO, which contributed only 2% of the cases. In our study, the meta-analysis HRs were not sensitive to back-extrapolation for NO_2. This approach relied on the assumption that the spatial distribution of the determinants of air pollution (eg, traffic, land use, and household density) had not changed substantially. We believe that the correlations between air pollution levels at the baseline residence and concentrations in earlier periods would be high, as it has been shown that spatial comparisons of NO_2 are stable over time [27,28], but we could not back-extrapolate all exposures and we recognize the potential for exposure misclassification. Furthermore, exposure at the baseline address does not necessarily cover the entire exposure time window of relevance for BC development, which seems to range from a few years [2] to many decades [13,29] before diagnosis, and we might have overlooked an association between exposure many decades ago and BC risk. Restriction of the study population to those who lived at the baseline address throughout follow-up provided similar null results (Supplementary Table 9). The lack of information on exposure before baseline and elsewhere (eg, at work and during transport) is a potential source of exposure misclassification that may have biased our results towards the null hypothesis. We have previously reported an association between ambient air pollution and lung cancer using the same methodology [9], which supports the notion that this method does capture exposures relevant for cancer development. However, we cannot rule out that an inadequate follow-up period coupled with some unavoidable misclassification of exposure could have masked any low-level BC risk associated with ambient air pollution exposure in the general population. It is not possible in this study to estimate latency, since exposure, which would have begun before baseline, was not estimated in our study. Nevertheless, subjects in our study were all aged >40 yr at baseline, and thus would have been exposed to air pollution for an adequate period of time to demonstrate a higher risk. Furthermore, we did find that active smoking recorded at baseline in all cohorts was associated with higher BC risk (adjusted HR ranging from 1.01 to 1.20 per g/d), which suggests that there was adequate follow-up time for these cohorts.

If our study participants had been older at baseline or had been followed for a longer time, more BC cases could be included to increase the precision of the risk estimates. Nonetheless, our study included 941 BC cases and provided results with very narrow confidence intervals. We adjusted the analyses for a number of potential confounding factors.

The small change in HR after adjustment was mainly due to smoking. The potential for residual confounding by smoking seems limited, since adjustment only affected HRs moderately and because similar null results were observed among never-smokers (Supplementary Table 8). Information on education was not available for the Austrian cohort, which contributed a third of the cases in our study. However, for all the other cohorts, the HRs associated with $PM_{2.5}$ and NO_2 exposure were similar with and without adjustment for education. Therefore, it seems unlikely that this may have caused substantial bias.

Furthermore, we did not assess effect modification by age at diagnosis and stage of disease, so we cannot exclude the possibility that the null effect of air pollution was impacted by age and/or restriction of the cases series to non–muscle-invasive BC. Finally, we cannot exclude confounding from potential risk factors for BC that were unaccounted for, such as disinfection by-products [30] or arsenic [31] in drinking water. Future studies should consider evaluation of polycyclic aromatic amines, which was not possible in our study.

5. Conclusions

In conclusion, this large prospective study does not provide evidence of an association between ambient air pollution at place of residence and BC incidence.

Author contributions: Marie Pedersen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Brunekreef, Beelen, de Hoogh, Hoek, Olsson, Korek, Eriksen, Marcon, Eeftens, Tsai, Ranzi, Cesaroni, Amiano, Nieuwenhuijsen, Sokhi, Aamodt, Wang.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euf.2016.11.008.

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