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ARTICLE

Long-term exposure to ambient air pollution and bladder cancer incidence in a pooled European cohort: the ELAPSE project

Jie Chen[1]✉, Sophia Rodopoulou[2], Maciej Strak[1,3], Kees de Hoogh[4,5], Tahir Taj[6], Aslak Harbo Poulsen[6], Zorana J. Andersen[7], Tom Bellander[8,9], Jørgen Brandt[10,11], Emanuel Zitt[12,13], Daniela Fecht[14], Francesco Forastiere[15,16], John Gulliver[14,17], Ole Hertel[18], Barbara Hoffmann[19], Ulla Arthur Hvidtfeldt[6], W. M. Monique Verschuren[3,20], Jeanette T. Jørgensen[7], Klea Katsouyanni[2,14], Matthias Ketzel[10,21], Anton Lager[22], Karin Leander[8], Shuo Liu[7], Petter Ljungman[8,23], Gianluca Severi[24,25], Marie-Christine Boutron-Ruault[24], Patrik K. E. Magnusson[26], Gabriele Nagel[27], Göran Pershagen[8,9], Annette Peters[28,29], Debora Rizzuto[30,31], Yvonne T. van der Schouw[20], Evangelia Samoli[2], Mette Sørensen[6,32], Massimo Stafoggia[8,15], Anne Tjønneland[6,33], Gudrun Weinmayr[27], Kathrin Wolf[28], Bert Brunekreef[1], Ole Raaschou-Nielsen[6,10,34] and Gerard Hoek[1,34]

BACKGROUND: The evidence linking ambient air pollution to bladder cancer is limited and mixed.
METHODS: We assessed the associations of bladder cancer incidence with residential exposure to fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), warm season ozone (O_3) and eight $PM_{2.5}$ elemental components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) in a pooled cohort ($N = 302{,}493$). Exposures were primarily assessed based on 2010 measurements and back-extrapolated to the baseline years. We applied Cox proportional hazard models adjusting for individual- and area-level potential confounders.
RESULTS: During an average of 18.2 years follow-up, 967 bladder cancer cases occurred. We observed a positive though statistically non-significant association between $PM_{2.5}$ and bladder cancer incidence. Hazard Ratios (HR) were 1.09 (95% confidence interval (CI): 0.93–1.27) per 5 μg/m^3 for 2010 exposure and 1.06 (95% CI: 0.99–1.14) for baseline exposure. Effect estimates for NO_2, BC and O_3 were close to unity. A positive association was observed with $PM_{2.5}$ zinc (HR 1.08; 95% CI: 1.00–1.16 per 10 ng/m^3).
CONCLUSIONS: We found suggestive evidence of an association between long-term $PM_{2.5}$ mass exposure and bladder cancer, strengthening the evidence from the few previous studies. The association with zinc in $PM_{2.5}$ suggests the importance of industrial emissions.

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[1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands. [2]Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece. [3]National Institute for Public Health and the Environment, Bilthoven, the Netherlands. [4]Swiss Tropical and Public Health Institute, Basel, Switzerland. [5]University of Basel, Basel, Switzerland. [6]Danish Cancer Society Research Center, Copenhagen, Denmark. [7]Section of Environment and Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark. [8]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [9]Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden. [10]Department of Environmental Science, Aarhus University, Roskilde, Denmark. [11]iClimate – interdisciplinary Centre for Climate Change, Aarhus University, Roskilde, Denmark. [12]Agency for Preventive and Social Medicine (aks), Bregenz, Austria. [13]Department of Internal Medicine 3, LKH Feldkirch, Feldkirch, Austria. [14]MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK. [15]Department of Epidemiology, Lazio Region Health Service/ASL Roma 1, Rome, Italy. [16]Environmental Research Group, School of Public Health, Faculty of Medicine, Imperial College, London, UK. [17]Centre for Environmental Health and Sustainability & School of Geography, Geology and the Environment, University of Leicester, Leicester, UK. [18]Departments of Bioscience, Aarhus University, Roskilde, Denmark. [19]Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [20]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [21]Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford GU2 7XH, United Kingdom. [22]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden. [23]Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden. [24]University Paris-Saclay, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP UMR1018, 94805 Villejuif, France. [25]Department of Statistics, Computer Science and Applications "G. Parenti" (DISIA), University of Florence, Florence, Italy. [26]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [27]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany. [28]Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany. [29]Chair of Epidemiology, Ludwig Maximilians Universität München, Munich, Germany. [30]Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden. [31]Stockholm Gerontology Research Center, Stockholm, Sweden. [32]Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark. [33]Diet, Genes and Environment (DGE), Bonn, Germany. [34]These authors contributed equally: Ole Raaschou-Nielsen, Gerard Hoek. ✉email: j.chen1@uu.nl

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INTRODUCTION

The International Agency for Research on Cancer (IARC) classified outdoor air pollution and particulate matter (PM) from outdoor air pollution as carcinogenic to humans [1]. The classification was largely based on associations of outdoor air pollution and lung cancer, whereas some evidence for urinary bladder cancer was also noted. Bladder cancer is one of the most common cancers and among the leading causes of cancer death worldwide. According to the Global Burden of Disease Study (GBD) 2019, bladder cancer accounted for 2.2%, 2.3% and 1.8% of the global neoplasm incident cases, deaths and disability-adjusted life-years (DALYs), respectively [2].

Studies have associated air pollution and increased bladder cancer risks in occupational settings, where workers were exposed to high concentrations of, for example, polycyclic aromatic hydrocarbons (PAHs) and diesel exhaust [3–6]. So far, few studies have investigated residential exposure to ambient air pollution in the general population in relation to bladder cancer, and the results are mixed. In the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) analyses, bladder cancer mortality was significantly positively associated with residential exposure to particulate mater with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), whereas weak, statistically non-significant associations were fou`nd with nitrogen dioxide (NO_2) or ozone (O_3) exposure [7]. The National Health Interview Survey (NHIS) also reported a significantly positive association between residential $PM_{2.5}$ exposure and bladder cancer mortality [8]. However, no association was found for incident bladder cancer risks with residential exposure to $PM_{2.5}$ or NO_2 in the Spanish Bladder cancer study [9] and the European Study of Cohorts for Air Pollution Effects (ESCAPE) study [10].

As outdoor air pollution is a mixture of pollutants originating from multiple sources, studies also attempted to identify the most responsible air pollution sources for the potential bladder cancer risks. A limited number of studies have evaluated markers of traffic and industrial sources, with inconsistent findings. A statistically non-significant positive association between bladder cancer incidence and nitrogen oxide (NO_x), as a proxy for traffic-related air pollution, was found in the Danish Diet Cancer and Health (DCH) cohort [11], as well as in a cohort of 9816 coronary intervention patients in Israel [12]. No clear evidence was found for an association between residence along main roads and bladder cancer incidence in Amsterdam, using traffic intensity as a surrogate exposure [13]. In an earlier analysis within the Spanish Bladder cancer study, several surrogate indices of air pollution from industrial emissions were found to be positively associated with bladder cancer [14]. Hydrogen sulfide (H_2S) from a contaminated landfill site in Rome was associated with increased risk of bladder cancer mortality in females [15]. However, the association was sensitive to the adjustment for other pollutants. In ESCAPE, exposure to NO_x, black carbon (BC), organic carbon (OC) and several elemental components were assessed to represent different air pollution sources [10], but none was associated with bladder cancer incidence.

To add to the limited evidence on the associations between ambient air pollution and bladder cancer incidence in general population, we conducted analyses in a large pooled cohort within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project [16]. ELAPSE builds on the ESCAPE collaboration by pooling data from selected cohorts and extending the follow-up period. In addition, we strengthened exposure assessment which allowed better coverage of included cohorts in ELAPSE. In the present study, we assessed the associations between bladder cancer incidence and long-term exposure to $PM_{2.5}$, NO_2, BC and O_3. We further explored potential bladder cancer risks with specific elemental components in $PM_{2.5}$, in an attempt to identify the most responsible air pollution sources.

METHODS

Study population

Within the ELAPSE collaboration, we pooled data from eight cohorts across six European countries. Cohorts were selected if they contributed to analysis of low-level air pollution, were recruited relatively recently and were able to share data for pooling. Detailed information of each individual cohort was described previously [17, 18]. Of these eight cohorts, six contained information on bladder cancer incidence and the most important potential confounders. These six cohorts are: the *Cardiovascular Effects of Air Pollution and Noise in Stockholm* (CEANS) cohort in Sweden [19–22], the *Diet, Cancer and Health cohort* (DCH) in Denmark [23], the *Danish Nurse Cohort* (DNC) in Denmark [24], the *European Prospective Investigation into Cancer and Nutrition-Netherlands* (EPIC-NL) cohort in the Netherlands [25], the *Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* (E3N) in France [26], and the *Vorarlberg Health Monitoring and Prevention Programme* (VHM&PP) in Austria [27] (Table 1). Except for the DNC, all other subcohorts were part of ESCAPE. All included cohort studies were approved by the medical ethics committees in their respective countries. Each individual cohort prepared data according to a joint ELAPSE codebook and then transferred the data to Utrecht University. Data were pooled after careful checking and stored on a secure server.

Exposure assessment

We investigated exposure to $PM_{2.5}$, NO_2, BC, warm season O_3 (hereafter referred to as O_3) and eight a priori selected $PM_{2.5}$ elemental components in the present study. The eight components were selected in the ESCAPE study to represent major pollution sources in Europe: copper (Cu), iron (Fe) representing non-tailpipe traffic emissions; zinc (Zn) representing industrial emissions primarily; sulfur (S) representing long-range transport of secondary inorganic aerosols; nickel (Ni) and vanadium (V) representing mixed oil burning/industry; silicon (Si) representing crustal material; and potassium (K) representing biomass burning [28, 29].

We assessed 2010 annual average air pollution exposures with Europe-wide hybrid LUR models [30, 31], which incorporated ground-based measurements, satellite-derived estimates, chemical transport model estimates, land-use, road and population density data. The modelling of $PM_{2.5}$, NO_2 and O_3 exposures was based on the European Environmental Agency AirBase routine monitoring data [30], whereas the modelling of BC [30] and elemental composition exposures [31] was based on the standardised ESCAPE monitoring data. The hybrid LUR models were developed using supervised linear regression (SLR) and validated with five-fold hold-out validation. The models explained a moderate to large fraction of the measured concentration variation at the European scale (i.e. 66% for $PM_{2.5}$, 58% for NO_2, 51% for BC, 60% for O_3 and 41% to 79% across elemental components). Exposure models for $PM_{2.5}$ elemental composition were also developed with the Random Forest (RF) algorithm. The RF models consistently outperformed the SLR models at the European scale, whereas the SLR and RF models explained within-area variability similarly [31]. In the present study, we primarily exploited within-cohort exposure contrasts and thus interpreted the SLR and RF models equally. The exposure models were applied to create 100 × 100 m grids of the predicted air pollution concentrations covering the entire study area. Exposure to air pollution was assigned to participants' baseline residential addresses. We truncated negative elemental composition exposure predictions to zero, and a few unrealistically high exposure predictions to a maximum modelled concentration for each element [31]. Truncation was performed for SLR-modelled exposures (mostly to negative predictions): 12.9% for Cu, 0.6% for Fe, 14.1% for Ni, 16.8% for V and 3.4% for Zn. No truncation was needed for RF-modelled exposures.

We selected 2010 as the primary year of exposure modelling because 2009–2010 was the period of ESCAPE monitoring, which we used to develop BC and $PM_{2.5}$ composition models [30, 31]. For $PM_{2.5}$, this was the earliest year of a sufficiently wide coverage of $PM_{2.5}$ monitoring across Europe [30]. For consistency, we used year 2010 for NO_2 and O_3 as well. This analysis assumes that the spatial contrast of the relevant pollution concentrations remained reasonably stable from the baseline period (years 1985–2005, Table 1) to 2010 [30].

For $PM_{2.5}$, NO_2, BC and O_3, we also estimated exposures at each individual's baseline year using back-extrapolation. Back-extrapolation was performed by using estimated concentrations from the Danish Eulerian Hemispheric Model (DEHM) [32]. DEHM modelled predictions of monthly average concentrations across Europe at 26 × 26 km spatial resolution back

Table 1. Characteristics of the study population at baseline.

Subcohort[a]	Population size[b]	N persons in model 3 (%)	Baseline period	Follow-up	Average years of follow-up	Bladder cancer cases, N	Age at baseline (mean ± SD)	Percent female	Percent current smokers	No. of cigarettes/day[c] (mean ± SD)	Years of smoking[c] (mean ± SD)
Pooled cohort	367,404	302,493 (82.3)	–	–	18.2	967	48.2 ± 13.4	66	24	15.1 ± 8.9	25.2 ± 13.1
CEANS-SDPP	7835	7305 (93.2)	1992–1998	2011	15.3	21	47.0 ± 4.9	59	26	13.6 ± 7.4	27.8 ± 8.6
CEANS-SIXTY	4180	3660 (87.6)	1997–1999	2014	12.0	27	60.0 ± 0.0	50	21	13.3 ± 7.7	36.2 ± 10.1
CEANS-SALT	6724	5625 (83.7)	1998–2003	2011	9.9	26	57.3 ± 10.4	53	21	12.7 ± 8.1	37.6 ± 9.1
CEANS-SNACK	3248	2359 (72.6)	2001–2004	2011	7.0	12	72.5 ± 10.4	62	15	11.7 ± 8.3	43.2 ± 13.5
DCH	56,308	52,779 (93.7)	1993–1997	2015	16.9	301	56.7 ± 4.4	53	36	16.5 ± 9.0	36.3 ± 7.7
DNC-1993	19,664	15,556 (79.1)	1993	2013	16.9	50	56.0 ± 8.3	100	37	13.8 ± 8.1	31.4 ± 9.9
DNC-1999	8769	7430 (84.7)	1999	2013	13.0	2	47.9 ± 4.1	100	28	13.3 ± 7.4	27.1 ± 7.1
EPIC-NL-Morgen	20,711	17,792 (85.9)	1993–1997	2013	16.4	46	42.7 ± 11.2	54	35	15.7 ± 8.6	24.5 ± 10.6
EPIC-NL-Prospect	16,194	13,640 (84.2)	1993–1997	2013	15.7	33	57.6 ± 6.0	100	23	13.6 ± 8.7	36.7 ± 7.7
E3N	53,521	36,258 (67.7)	1989–1991	2011	15.9	52	52.8 ± 6.7	100	13	11.3 ± 9.1	28.5 ± 7.6
VHM&PP	170,250	140,089 (82.3)	1985–2005	2014	21.0	397	41.7 ± 14.9	56	20	15.6 ± 8.9	13.4 ± 8.2

[a]The Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort (consisting four subcohorts: the *Stockholm Diabetes Prevention Program* (SDPP) [19], the *Stockholm Cohort of 60-year-olds* (SIXTY) [22], the *Stockholm Screening Across the Lifespan Twin study* (SALT) [21] and *the Swedish National Study on Aging and Care in Kungsholmen* (SNAC-K) [20]) is in Sweden; the Diet, Cancer and Health cohort (DCH) is in Denmark; the Danish Nurse Cohort (DNC) (consisting of two surveys conducted in 1993 and 1999) is in Denmark; the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort is in the Netherlands (including the *Monitoring Project on Risk Factors* and *Chronic Diseases in the Netherlands* (MORGEN) and Prospect); the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) is in France; the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) is in Austria.

[b]Population size is the number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort

[c]For current smokers

to at least 1990 were obtained. We compared temporal patterns of DEHM-modelled concentrations and ground-based measurements for countries with monitoring data [30]. To allow different spatial trends within Europe, we calculated population weighted average concentrations at the Nomenclature of territorial units for statistics (NUTS-1) spatial scale for application to the national cohorts. NUTS-1 reflects major socio-economic regions (e.g. four regions in the Netherlands and 14 regions in France). For smaller study areas, we calculated population weighted average concentrations within the study area. We back-extrapolated concentrations using both a difference and a ratio method with 2010 as the baseline. With the difference method, the concentration difference between a year and 2010 from the DEHM model is added to all cohort exposures for that year. With the ratio method, the concentration ratio between a year and 2010 from the DEHM model is used to multiply all cohort exposure for that year. We were not able to estimate exposures to $PM_{2.5}$ elemental components at baseline years, because we had insufficient information on the elemental composition concentration in Europe over time.

Outcome

For all cohorts, except E3N, cancer diagnosis data were obtained from national cancer registries. In E3N, cancer was identified by self-reports from biannual questionnaires, which were confirmed through pathological reports and reviewed by an oncologist, or from death certificates. Bladder cancer incidence was defined as the first primary diagnosis during the follow-up, according to the *International Classification of Diseases, Ninth Revision* (ICD-9) code 188 and the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) code C67. Participants with any cancer diagnoses (except non-melanoma skin cancer) before baseline were excluded.

Statistical analyses

Main analyses. We applied Cox proportional hazards models to estimate associations between long-term air pollution exposures and bladder cancer incidence, following the common ELAPSE analytical framework [33, 34]. In the Cox models, we stratified by subcohorts because the assumption of proportional hazards did not hold for subcohorts. Using strata to account for between-cohort heterogeneity implies that we mostly evaluate within-cohort exposure contrasts. Each air pollutant was included as a linear term in the Cox models. Hazard ratios (HRs) and 95% CIs were calculated with a fixed increment for each pollutant following the increments selected in previous ESCAPE and ELAPSE publications [17, 18, 35]: $PM_{2.5}$—5 μg/m^3, NO_2—10 μg/m^3, BC—0.5×10^{-5}/m, O_3—10 μg/m^3, $PM_{2.5}$ Cu—5 ng/m^3, $PM_{2.5}$ Fe—100 ng/m^3, $PM_{2.5}$ K—50 ng/m^3, $PM_{2.5}$ Ni—1 ng/m^3, $PM_{2.5}$ S—200 ng/m^3, $PM_{2.5}$ Si—100 ng/m^3, $PM_{2.5}$ V—2 ng/m^3, $PM_{2.5}$ Zn—10 ng/m^3. Censoring occurred at the time of any cancer other than bladder cancer diagnosis (except non-melanoma skin cancer), death, emigration, loss to follow-up or end of follow-up, whichever came first. We specified three confounder models with increasing adjustment for individual- and area-level covariates: Model 1 included age (as the time axis), subcohort (as strata), sex (as strata), and year of enrollment (as a continuous variable); Model 2 further adjusted for individual-level covariates, including marital status (married/cohabiting, divorced/separated, single, widowed), smoking status (never, former, current), smoking duration (years of smoking) and smoking intensity (cigarettes/day) for current smokers, squared smoking intensity, body mass index (BMI) in categories (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2), and employment status (employed vs. unemployed); Model 3 (main model) further adjusted for area-level mean income in 2001 (as a continuous variable). The spatial scale of area varied from smaller neighbourhoods and city districts (CEANS, EPIC-NL, E3N) to municipalities (DCH, DNC, VHM&PP). Participants with missing exposure or incomplete information on Model 3 covariates were excluded from all analyses to ensure comparability among the model results.

Two-pollutant models were specified for all combinations of $PM_{2.5}$, NO_2, BC and O_3 to assess the robustness of effect estimates for one pollutant to inclusion of another. Two-pollutant models for elemental composition were analysed with $PM_{2.5}$ or NO_2 as the second pollutant. We adjusted for $PM_{2.5}$ to investigate whether the association with individual elemental components remained after adjustment for generic $PM_{2.5}$ mass [36]; we adjusted for NO_2 in an attempt to disentangle the individual component effect from traffic exhaust emission for which NO_2 is used as a marker.

Additional analyses. Given the fact that cancer development is usually a long process, the choice of the exposure period may be critical and is often

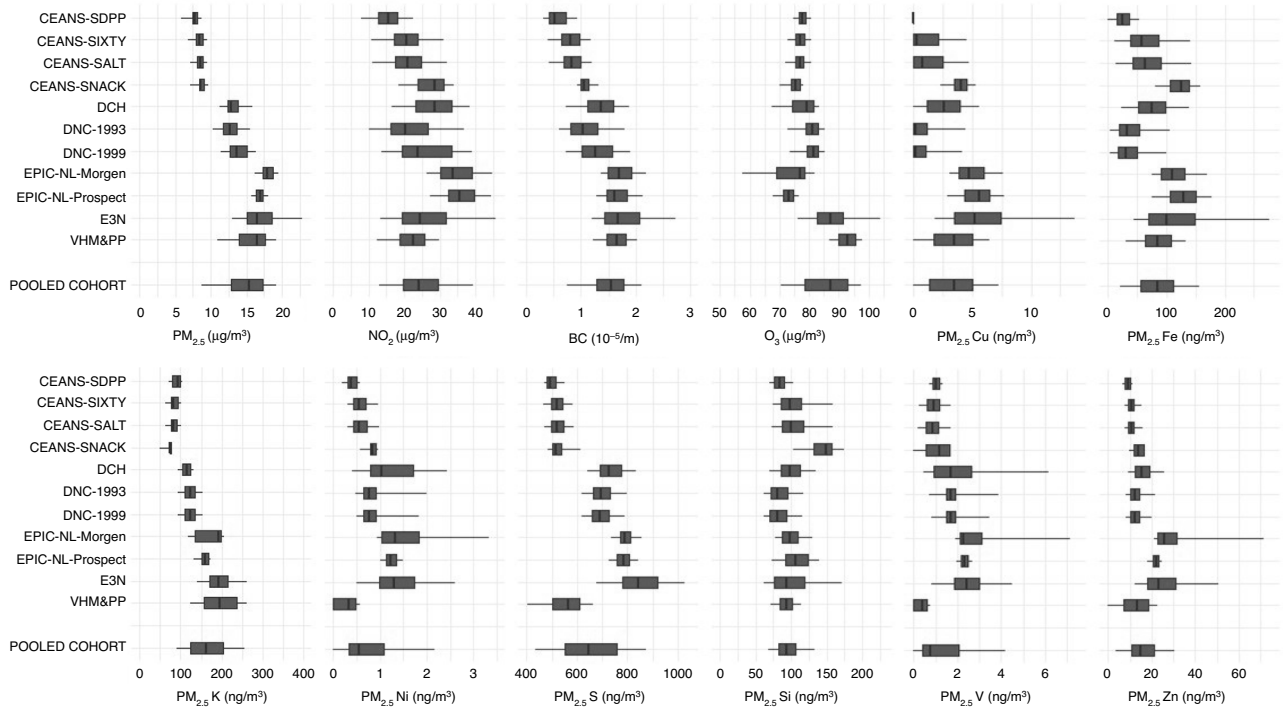

Fig. 1 Exposure distribution (corresponding values shown in Table S1). The boundary of the box closest to zero indicates P25; furthest from zero—P75; bold vertical line inside the box—P50; whiskers indicate P5 and P95. Subcohorts are shown from north to south. Exposures were estimated with supervised linear regression. Elemental composition exposure estimated with random forest are shown in Fig. S1.

discussed in air pollution and cancer research [37]. We therefore applied exposures back-extrapolated to baseline years as described above to assess the sensitivity of our findings to using the 2010 exposures. To assess the sensitivity of our findings to potential residual confounding, we further adjusted for smoking in former smokers, education level, occupational status and alcohol assumption in cohorts that had such information. To assess the impact of individual cohorts on the effect estimates, we assessed the effect estimates by excluding one cohort at a time. We also assessed the associations between the four main pollutants and bladder cancer incidence in individual cohorts, acknowledging that the low number of cases in most cohorts may result in imprecise effect estimates. To evaluate the potential bias introduced by excluding participants with missing information on Model 3 covariates, we fitted Model 1 and Model 2 with participants with complete information on model 1 and model 2 covariates respectively.

We assessed the shape of the concentration-response functions (CRFs) for air pollution exposure and bladder cancer incidence with natural cubic splines with three degrees of freedom. We performed subset analyses for $PM_{2.5}$, NO_2, BC and O_3 exposures by restricting the main Model 3 analyses to participants with exposure level below certain cut-off values.

We evaluated effect modification by age at baseline (<65 vs. ≥65 years), sex and smoking status. For age categories and smoking status, we introduced an interaction term with air pollution into the model; for sex, we replaced the strata term by an interaction term with air pollution. We performed the Wald test to examine the differences in HRs between groups.

For elemental composition, we performed analyses with exposures estimated with SLR and RF models and interpreted results of the two exposure methods equally. We presented most elemental composition analyses with the SLR-modelled exposures in the main text because $PM_{2.5}$, NO_2, BC and O_3 exposures assigned to the cohorts were only estimated with SLR models [30]. In a subsequent analysis, we documented that, for $PM_{2.5}$ and NO_2 separately, SLR and RF models performed similarly, and had highly correlated predictions at randomly selected external validation sites ($PM_{2.5}$: Pearson $r = 0.89$; NO_2: $r = 0.93$) [38]. The SLR models are further more comparable to the LUR models used in the ESCAPE study [10].

All analyses were performed in R version 3.4.0 using packages: *survival, coxme, Matrix, foreach, glmnet, multcomp, survey, splines, Hmisc, mfp, VIM, ggplot2, frailtySurv, survsim, eha, stamod, metafor*. Statistical significance was based on a 95% confidence interval of effect estimate not including unity.

RESULTS

After excluding 17.7% of the total population, the pooled study consisted of 302,493 individuals, of whom 967 developed bladder cancers during 5,505,372 person-years of follow-up (Table 1). The exclusions were due to fail in logical checks (e.g. date of death before date of cancer diagnosis; 0.9%), cancer diagnosis before baseline (2.9%), missing exposure (0.5%), missing individual-level covariates (12.5%) or area-level mean income (0.9%). Most of the cohorts started in the 1990s and had follow-up untill 2011–2015. The largest subcohort was VHM&PP, which contributed more than half of the total person-years. Mean age of the participants at baseline ranged from 41.7 years to 72.5 years. Four subcohorts included female participants only and the pooled cohort comprised 66% women. Current smoker prevalence at baseline ranged from 13% to 37% with mean smoking duration ranging from 13.4 years to 43.2 years across subcohorts.

Figure 1 and Table S1 show the SLR-modelled air pollution exposure distribution in each subcohort. The exposure concentrations were generally lower in the North European cohorts than in more Southern cohorts. The within-cohort exposure contrast was substantial for NO_2, BC, Cu, Fe, Si and more limited for $PM_{2.5}$, O_3, K, Ni, S, V and Zn. Exposure distribution for elemental composition estimated with RF models is presented in Figure S1. We observed similar north-south concentration gradient for RF-modelled exposures. For most elements, the within-cohort exposure contrasts were smaller for RF- than SLR-modelled exposures. For $PM_{2.5}$, NO_2, BC and O_3, exposures back-extrapolated to baseline years are shown in Fig. S2. The baseline $PM_{2.5}$ exposures were higher and more variable than the 2010-exposure, whereas the baseline exposures to NO_2, BC and O_3 were similar or mildly higher than the 2010-exposure.

Table 2. Associations between main air pollutants and bladder cancer incidence in single- and two-pollutant models.

Exposure	Single pollutant HR	Two-pollutant model			
		HR adjusted for $PM_{2.5}$	HR adjusted for NO_2	HR adjusted for BC	HR adjusted for O_3
$PM_{2.5}$	1.09 (0.93, 1.27)	–	1.13 (0.93, 1.37)	1.16 (0.94, 1.41)	1.12 (0.93, 1.34)
NO_2	1.01 (0.91, 1.12)	0.96 (0.84, 1.10)	–	1.06 (0.84, 1.34)[a]	1.01 (0.89, 1.16)
BC	1.00 (0.90, 1.11)	0.94 (0.82, 1.07)	0.94 (0.74, 1.20)[a]	–	0.99 (0.87, 1.13)
O_3	1.00 (0.87, 1.14)	1.05 (0.89, 1.23)	1.01 (0.84, 1.21)	0.99 (0.83, 1.18)	–

Population size = 302,493; person-years at risk = 5,505,372; number of incident bladder cancer = 967; hazard ratio (95% confidence interval) presented for the following increments: $PM_{2.5}$—5 μg/m^3, NO_2—10 μg/m^3, BC—0.5×10^{-5}/m, O_3—10 μg/m^3; main model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 area-level mean income.
[a]Two-pollutant models of BC and NO_2 are difficult to interpret because of high correlation (average of cohort-specific spearman correlation coefficients of 0.81) between BC and NO_2 (Table S2).

In most subcohorts, exposure to $PM_{2.5}$ was moderately correlated with exposure to BC and NO_2 (Table S2). The correlations between NO_2 and BC were high in most subcohorts. O_3 exposures were negatively correlated with $PM_{2.5}$, NO_2 or BC. Correlations of elemental composition with $PM_{2.5}$ were mostly low to moderate (Table S3). Correlations with NO_2 were mostly high for Cu and Fe in subcohorts (Table S4). Correlations between air pollutants differed substantially in magnitude across cohorts, reflecting differences in study area size and presence of major sources. We focused on within-cohort correlations as the epidemiological analysis exploited mostly within-cohort exposure contrasts.

Associations between air pollution and bladder cancer

In the linear models, air pollution effect estimates were generally higher in the minimally adjusted models (Model 1, Table S5). HRs were mildly attenuated after adjusting for individual-level covariates (Model 2), and remained stable with further adjustment for area-level income (Model 3). The effect estimates were generally similar in Model 1 and Model 2, comparing the population with complete information on the corresponding model covariates and the population with complete data on Model 3 covariates, respectively, suggesting little selection bias was introduced by excluding participants with missing covariates (Table S5). In the fully adjusted models, we observed a positive but statistically nonsignificant association between $PM_{2.5}$ exposure and bladder cancer incidence (Table 2). The HRs for $PM_{2.5}$ remained stable in two-pollutant models with adjustment for NO_2, BC or O_3, with wider CIs. No association was evident for NO_2, BC or O_3. For elemental composition estimated with SLR models, we observed positive associations for K, S, Si and Zn, which was only statistically significant for Zn (Table 3). The HRs for K and Zn remained stable in two-pollutant models after adjusting for $PM_{2.5}$ or NO_2, with slightly wider CIs. The HRs for S and Si attenuated to unity after adjustment for $PM_{2.5}$. For RF-modelled elemental composition, we observed similar patterns for HRs for K, S, Si and Zn, except that HR for Si remained stable after adjusting for $PM_{2.5}$ (Table S6). Effect estimates were larger for elemental exposures estimated with RF models compared to SLR models, probably because of the generally smaller exposure contrasts for RF predictions. In two-pollutant models with adjustment for elemental composition, HRs for $PM_{2.5}$ remained stable after adjusting for S or Si, whereas the HRs attenuated after adjusting for K and Zn (Table S7). HRs for $PM_{2.5}$ in two-pollutant models with Zn were close to unity.

The sensitivity analyses did not alter the main findings. HRs for $PM_{2.5}$ back-extrapolated to baseline years attenuated mildly with narrower CIs compared to 2010 exposures (Table 4). The increased precision in HR was especially evident for back-extrapolated exposure using ratio method, as the exposure contrasts increased.

Table 3. Associations between $PM_{2.5}$ composition and bladder cancer incidence in single- and two-pollutant models.

Exposure	Single pollutant HR	Two-pollutant model	
		HR adjusted for $PM_{2.5}$	HR adjusted for NO_2
$PM_{2.5}$ Cu	0.99 (0.84, 1.17)	0.89 (0.71, 1.11)	0.94 (0.71, 1.26)
$PM_{2.5}$ Fe	0.98 (0.81, 1.17)	0.88 (0.70, 1.10)	0.86 (0.60, 1.22)
$PM_{2.5}$ K	1.06 (0.96, 1.16)	1.04 (0.92, 1.17)	1.06 (0.96, 1.17)
$PM_{2.5}$ Ni	0.93 (0.81, 1.06)	0.88 (0.76, 1.03)	0.89 (0.75, 1.05)
$PM_{2.5}$ S	1.06 (0.88, 1.27)	0.97 (0.75, 1.27)	1.07 (0.85, 1.35)
$PM_{2.5}$ Si	1.10 (0.77, 1.55)	1.02 (0.69, 1.49)	1.15 (0.70, 1.90)
$PM_{2.5}$ V	0.97 (0.87, 1.09)	0.95 (0.84, 1.07)	0.96 (0.85, 1.08)
$PM_{2.5}$ Zn	1.08 (1.00, 1.16)	1.07 (0.98, 1.17)	1.09 (1.00, 1.19)

Population size = 302,493; person-years at risk = 5,505,372; number of incident bladder cancer = 967; hazard ratio (95% confidence interval) presented for the following increments: $PM_{2.5}$ Cu—5 ng/m^3, $PM_{2.5}$ Fe—100 ng/m^3, $PM_{2.5}$ K—50 ng/m^3, $PM_{2.5}$ Ni—1 ng/m^3, $PM_{2.5}$ S—200 ng/m^3, $PM_{2.5}$ Si—100 ng/m^3, $PM_{2.5}$ V—2 ng/m^3, $PM_{2.5}$ Zn—10 ng/m^3; main model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 area-level mean income.
Exposures were estimated with supervised linear regression; effect estimates for elemental composition exposures estimated with random forest are shown in Table S6; effect estimates for $PM_{2.5}$ and NO_2 in two-pollutant models are shown in Table S7.

For NO_2, BC and O_3, effect estimates with baseline exposure were essentially unity. The effect estimates were stable with additional adjustment for smoking intensity and duration in former smokers, education, occupational status and alcohol assumption in cohorts that had such information (Table S8). The effect estimates were generally stable in analyses where we excluded one cohort at a time (Fig. S3). The 95% CIs widen after excluding the large VHM&PP cohort, which contributed more than half of the person-years. For some pollutants, the HR point estimates increased or decreased when dropping the VHM&PP with the 95% CIs including unity. The uncertainty of HRs in most individual cohorts is large because of the small number of cases (Fig. S4).

We generally observed a linear increase in the exposure-response function in the lower end of the exposure distribution (Fig. S5). For some pollutants, the CRFs showed a decreasing trend with wide CIs at the end of the curve, where observations were few and shapes, therefore, were difficult to interpret. A positive association was found at low levels of NO_2, decreasing at levels where the density of data was still sizable, which was difficult to interpret. Subset analyses showed increased risks for bladder cancer incidence when restricting to $PM_{2.5}$ concentrations below

Table 4. Associations between air pollutants and bladder cancer incidence using baseline exposures.

Exposure	2010 exposure	Baseline (ratio)[a]	Baseline (difference)[a]
$PM_{2.5}$	1.09 (0.93, 1.27)	1.06 (0.99, 1.14)	1.08 (0.97, 1.20)
NO_2	1.01 (0.91, 1.12)	1.02 (0.95, 1.09)	1.02 (0.92, 1.12)
BC	1.00 (0.90, 1.11)	1.01 (0.94, 1.09)	1.01 (0.92, 1.12)
O_3	1.00 (0.87, 1.14)	0.97 (0.86, 1.09)	0.97 (0.86, 1.10)

Population size = 302,472; person-years at risk = 5,505,372; number of incident bladder cancer = 967; hazard ratio (95% confidence interval) presented for the following increments: $PM_{2.5}$—5 μg/m^3, NO_2—10 μg/m^3, BC—0.5×10^{-5}/m, O_3—10 μg/m^3; main model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 area-level mean income.
[a]Exposure back-extrapolated to baseline years using ratio and difference methods, respectively.

15 μg/m^3 exposures with wider CIs as the cancer cases became fewer (Table S9). For NO_2, positive associations were found when excluding the highest NO_2 exposures, consistent with the CRF. There was no clear evidence for effect modification by age group or smoking status. Effect estimates tended to be higher in participants with baseline age < 65 y and current smokers, but the differences were not statistically significant (Table S10). HRs for $PM_{2.5}$ were significantly higher for male than female, which could be due to residual confounding by smoking.

DISCUSSIONS

We observed a positive though statistically non-significant association between long-term $PM_{2.5}$ exposure and bladder cancer incidence in a pooled cohort of more than 300,000 participants across Europe. In particular, zinc in $PM_{2.5}$ was statistically positively associated with bladder cancer incidence. The associations were robust to adjustment for other pollutants and several sensitivity analyses.

Two previous cohort studies reported significantly positive associations between $PM_{2.5}$ exposure and bladder cancer mortality in the United States. Translating to a 5 μg/m^3 increase in $PM_{2.5}$ (the exposure contrast used in our analyses), HRs of 1.15 (95% CI: 1.04–1.27) and 1.22 (95% CI: 1.00–1.48) were reported in the ACS CPS-II and the NHIS studies [7, 8]. We observed a lower HR (1.09, 95% CI: 0.93–1.27) for incident bladder cancer in the present study compared to the US studies. The HRs for bladder cancer mortality and incidence may not be directly comparable because cancer mortality reflects both disease incidence and survival following diagnosis. The 5-year survival rate for people diagnosed with bladder cancer is relatively high (i.e. average of 77% for bladder cancer cases diagnosed during 2010 through 2016 in the U.S.) [39]. In a Hong Kong study where mortality from both kidney and bladder cancers were evaluated together, a null association (HR: 0.98, 95% CI: 0.58–1.64 per 10 μg/m^3 of $PM_{2.5}$) was reported [40]. The Spanish Bladder Cancer Study reported an OR of 1.06 (95% CI: 0.71–1.60) for the association between bladder cancer incidence and a 5.9 μg/m^3 increase in $PM_{2.5}$, using a case-control study design [9]. In the ESCAPE study, a negative association with $PM_{2.5}$ was reported with a wide CI (HR per 5 μg/m^3 = 0.86, 95% CI: 0.63, 1.18) [10]. We did not attach too much importance to the negative point estimate given the wide CI. Built on the ESCAPE cohorts, the present study observed a narrower CI for $PM_{2.5}$ effect estimate, which may relate to the longer follow-up and the conduct of a pooled analysis. The differences in effect estimates reported in ESCAPE and ELAPSE could also be explained by the somewhat different cohorts included. However, low heterogeneity across cohorts was observed in ESCAPE [10] and our results remained stable in sensitivity analysis when dropping one cohort at a time. All of the above mentioned studies adjusted for tobacco smoking in the statistical analyses, as smoking is the primary risk factor for bladder cancer [41]. There was no clear evidence of effect modification by smoking status in the Spanish Bladder Cancer Study [9] and the ACS CPS-II [7], whereas the NHIS reported significantly higher bladder cancer risks associated with $PM_{2.5}$ among current smokers [8]. We observed a stronger though statistically non-significant association with $PM_{2.5}$ among current smokers compared to never smokers, suggesting there might be some residual confounding by smoking even after adjustment for smoking status, duration and intensity in the present study. The small difference in HRs between models adjusted for smoking and other lifestyle factors with age-sex adjusted models, suggests confounding by smoking was likely limited.

Ambient air pollution may promote bladder cancer through generic mechanisms such as inflammation and oxidative stress [1]. Besides that, air pollution also contains PAHs, dioxins and sulfur-containing compounds, which are known mutagens and/or carcinogens and could cause bladder cancers [42, 43]. Studies have linked occupational exposure to PAHs with higher risks of bladder cancers [5]. Higher bladder cancer risks have also been related to occupational exposure to high concentrations of diesel-engine exhaust [4, 44]. The IARC concluded 'sufficient evidence' for the carcinogenicity of diesel-engine exhaust in humans [45]. Diesel engines are used for on-road and non-road transport and (heavy) equipment in various industrial sectors. Over the past decades, diesel-engine exhaust from on-road vehicles has decreased substantially in North America and Europe because of the adoption of tight emission standards. However, emissions from non-road applications (e.g. industries) are still largely uncontrolled. In Western Europe, increased risks of bladder cancer were found for metal workers and machinists [5]. Associations in general populations are less clear.

In the present study, we found no evidence of associations between traffic-related air pollution and bladder cancer incidence, reflected by effect estimates close to unity for proxies of tailpipe emission (BC and NO_2) and non-tailpipe emission such as brake, tyre and road abrasions (Cu and Fe in $PM_{2.5}$). We also did not find evidence that traffic-related air pollution was associated with lung cancer in the same study [18, 34]. Analyses in the Spanish Bladder cancer study, the ACS CPS-II and the ESCAPE also showed no associations between NO_2 exposure and bladder cancer risks [7, 9, 10]. The ESCAPE further documented null associations with bladder cancer incidence for NO_x, BC, traffic density, and Cu and Fe in PM [10]. In an earlier study conducted in Amsterdam, no evidence for an association between residential traffic density and bladder cancer incidence was found [13]. In the DCH cohort, which is a subcohort included in the current pooled analysis, a 100 ug/m^3 increase in NO_x was associated with an HR of 1.32 (95% CI: 0.80, 2.19) for bladder cancer incidence [11]. Analyses in an Israeli cohort of 9816 coronary intervention patients reported a similar magnitude of effect estimate with a much wider CI for bladder cancer incidence: an HR of 1.07 (0.83, 1.37) per 10-ppb increase in NO_x, translating to an HR of 1.40 (0.39, 4.83) per 100 μg/m^3 increase in NO_x [12]. We found positive associations between NO_2 and bladder cancer incidence only at low concentrations, decreasing at high NO_2 concentrations. The non-linear CRF was difficult to interpret and could be related to competing risks for other diseases that were not accounted for in the present study.

We found robust associations between bladder cancer incidence and Zn exposure in the present study. Zn was primarily related to industrial emissions in our exposure models, reflected by the large proportion of variation in measurements explained by predictors representing industrial Zn emission [31]. The observed associations could be due to Zn exposures per se, or other correlated components from industrial emissions. We did not observe consistently positive associations between bladder cancer incidence and exposure to Ni or V in the present study, which were selected to represent emission from mixed oil burning/industry [28, 29]. Both Ni and V are suggested to derived mainly from shipping emission in Europe [46], whereas Zn was considered as a source identifier for metals industry [47]. This is supported by ports from land-use being important predictors for our Ni and V models [31]. The correlations between Zn and Ni as well as Zn and V exposures were low to moderate in the present study (average of cohort-specific Spearman correlation coefficients ranged from 0.19 to 0.75)[17]. The earlier Spanish Bladder Cancer Study reported positive associations with bladder cancer for several indices of air pollution from industrial emissions [14]. The limitation of using exposure indices, such as proximity to industries, is that the air pollution concentrations cannot be quantitatively estimated. In an analysis within population residing in proximity of a coal-oil-fired thermal power plant in Italy, an increased risk of bladder cancer was related to higher exposure to benzene and NO_2 in women aged ≥75 y [48].

The main strength of this study is that we were able to pool data from six European cohorts with detailed individual- and area-level covariate information, including smoking. The pooling of data allowed for high statistical power to examine the association between air pollution exposure and the incidence of a rare cancer. Another strength is the application of centrally developed Europe-wide air pollution exposure models. Applying consistent exposure estimates for such a large international study facilitates the correct interpretation of results. Compared to ESCAPE, the Europe-wide exposure models were improved by additionally incorporating outputs from chemical transport models and satellite data representing the regional background concentrations for emissions from specific sources [30, 31, 49]. Thus the model specificity was increased, which helped to identify the health effects associated with specific air pollutants.

One limitation is that the exposure assessments were based on 2010 measurements whereas most included subcohorts started in the mid-1990s. We assumed that the spatial contrast of air pollution remained stable over the past decades, which was confirmed by several studies in Europe for NO_2 [50–52], suggesting little bias was introduced. Importantly, we observed robust associations when applying back-extrapolated exposures for $PM_{2.5}$, NO_2, BC and O_3. Unfortunately, we were not able to assess associations with back-extrapolated exposures for $PM_{2.5}$ elemental components because of the insufficient information of trends over time. We cannot rule out the possibility that spatial contrast for these air pollutants may have been less stable. Moreover, the generally moderate performance of the elemental models may limit our ability to detect a potential association. As the measurement errors introduced are likely nondifferential, the effect estimates are more likely to be biased toward null. Another limitation is that we were unable to account for residential mobility during follow-up and only have information on lifestyle factors at baseline, whereas the study population may move or change their smoking and other habits over time. We further cannot rule out the possibility of residual confounding by other missing covariates of potential interest, such as occupational exposures. We, however, observed robust results in sensitivity analyses with additional adjustment for occupational status or educational level in subsets of the pooled cohort.

CONCLUSIONS

This study showed suggestive evidence of an association between long-term exposure to $PM_{2.5}$ and bladder cancer incidence, strengthening the evidence from the few previous studies on $PM_{2.5}$. We also found associations with zinc in $PM_{2.5}$, which is primarily associated with industrial emissions. We found no association between traffic-related air pollution and bladder cancer.

DATA AVAILABILITY

The exposure maps are available on request from Dr Kees de Hoogh (c.dehoogh@swisstph.ch). The cohort data could only be pooled for the ELAPSE framework but is not available for sharing due to strict national data protection regulations and the General Data Protection Regulation of the European Union. The ELAPSE study protocol is available at http://www.elapseproject.eu/. A detailed statistical analysis plan is available on reasonable request from the corresponding author (j.chen1@uu.nl).

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AUTHOR CONTRIBUTIONS

GH, ORN and JC: study conceptualisation and design; GH and BB: principal investigators of the ELAPSE project; JC: statistical analysis and manuscript writing; GH, ORN and BB: supervision, manuscript review and editing; GH, BB, JC and MS: ELAPSE project coordination, preparing pooled data for analyses, and providing support with the access to pooled cohort data; SR, ES and KK: contribution of statistical analyses strategy and scripts for the statistical analyses; KdH, JC and GH: exposure assessment. All authors contributed to the interpretation of the results. All authors read and revised the manuscript for the important intellectual content and approved the final draft of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study involved no contact with members of the study population and the published results does not allow identification of individuals. The analyses were undertaken in a secure IT environment where no individual level data can be retrieved. All included cohort studies were approved by the medical ethics committees in their respective countries.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Jie Chen.

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