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

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214

215 **Authors' contributions**

216 G.H., O.R.N. and J.C.: study conceptualization and design; G.H. and B.B.: principal investigators of the
217 ELAPSE project; J.C.: statistical analysis and manuscript writing; G.H., O.R.N. and B.B.: supervision,
218 manuscript review and editing; G.H., B.B., J.C., and M.S.: ELAPSE project coordination, preparing
219 pooled data for analyses, and providing support with the access to pooled cohort data; S.R., E.S., and
220 K.K.: contribution of statistical analyses strategy and scripts for the statistical analyses; K.d.H., J.C., and
221 G.H.: exposure assessment. All authors contributed to the interpretation of the results. All authors
222 read and revised the manuscript for the important intellectual content and approved the final draft of
223 the manuscript.

224

225 **Ethics approval and consent to participate**

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

230

231 **Data availability**

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

237

238 **Competing Interests**

239 The authors declare no conflict of interest.

240

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247 **Abstract**

248 **Background** The evidence linking ambient air pollution to bladder cancer is limited and mixed.

249 **Methods** We assessed the associations of bladder cancer incidence with residential exposure to fine
250 particles (PM_{2.5}), nitrogen dioxide (NO₂), black carbon (BC), warm season ozone (O₃) and eight PM_{2.5}
251 elemental components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) in a pooled
252 cohort (N = 302,493). Exposures were primarily assessed based on 2010 measurements and back-
253 extrapolated to the baseline years. We applied Cox proportional hazard models adjusting for
254 individual- and area-level potential confounders.

255 **Results** During an average of 18.2 years follow-up, 967 bladder cancer cases occurred. We observed a
256 positive though statistically non-significant association between PM_{2.5} and bladder cancer incidence.
257 Hazard Ratios (HR) were 1.09 (95% confidence interval (CI): 0.93–1.27) per 5 µg/m³ for 2010 exposure
258 and 1.06 (95% CI: 0.99–1.14) for baseline exposure. Effect estimates for NO₂, BC and O₃ were close to
259 unity. A positive association was observed with PM_{2.5} zinc (HR 1.08; 95% CI: 1.00–1.16 per 10 ng/m³).

260 **Conclusions** We found suggestive evidence of an association between long-term PM_{2.5} mass exposure
261 and bladder cancer, strengthening the evidence from the few previous studies. The association with
262 zinc in PM_{2.5} suggests the importance of industrial emissions.

263

264 **Keywords** Air pollution, Particulate matter, Particle components, Long-term exposure, Bladder cancer

265 1. Introduction

266 The International Agency for Research on Cancer (IARC) classified outdoor air pollution and particulate
267 matter (PM) from outdoor air pollution as carcinogenic to humans (1). The classification was largely
268 based on associations of outdoor air pollution and lung cancer, whereas some evidence for urinary
269 bladder cancer was also noted. Bladder cancer is one of the most common cancers and among the
270 leading causes of cancer death worldwide. According to the Global Burden of Disease Study (GBD)
271 2019, bladder cancer accounted for 2.2%, 2.3% and 1.8% of the global neoplasm incident cases, deaths
272 and disability-adjusted life-years (DALYs), respectively (2).

273 Studies have associated air pollution and increased bladder cancer risks in occupational settings,
274 where workers were exposed to high concentrations of, for example, polycyclic aromatic
275 hydrocarbons (PAHs) and diesel exhaust (3-6). So far, few studies have investigated residential
276 exposure to ambient air pollution in the general population in relation to bladder cancer, and the
277 results are mixed. In the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) analyses,
278 bladder cancer mortality was significantly positively associated with residential exposure to particulate
279 matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), whereas weak, statistically non-significant
280 associations were found with nitrogen dioxide (NO₂) or ozone (O₃) exposure (7). The National Health
281 Interview Survey (NHIS) also reported a significantly positive association between residential PM_{2.5}
282 exposure and bladder cancer mortality (8). However, no association was found for incident bladder
283 cancer risks with residential exposure to PM_{2.5} or NO₂ in the Spanish Bladder cancer study (9) and the
284 European Study of Cohorts for Air Pollution Effects (ESCAPE) study (10).

285 As outdoor air pollution is a mixture of pollutants originating from multiple sources, studies also
286 attempted to identify the most responsible air pollution sources for the potential bladder cancer risks.
287 A limited number of studies have evaluated markers of traffic and industrial sources, with inconsistent
288 findings. A statistically non-significant positive association between bladder cancer incidence and
289 nitrogen oxide (NO_x), as a proxy for traffic-related air pollution, was found in the Danish Diet Cancer
290 and Health (DCH) cohort (11), as well as in a cohort of 9,816 coronary intervention patients in Israel
291 (12). No clear evidence was found for an association between residence along main roads and bladder
292 cancer incidence in Amsterdam, using traffic intensity as a surrogate exposure (13). In an earlier
293 analysis within the Spanish Bladder cancer study, several surrogate indices of air pollution from
294 industrial emissions were found to be positively associated with bladder cancer (14). Hydrogen sulfide
295 (H₂S) from a contaminated landfill site in Rome was associated with increased risk of bladder cancer
296 mortality in females (15). However, the association was sensitive to the adjustment for other

297 pollutants. In ESCAPE, exposure to NO_x, black carbon (BC), organic carbon (OC) and several elemental
298 components were assessed to represent different air pollution sources (10), but none was associated
299 with bladder cancer incidence.

300 To add to the limited evidence on the associations between ambient air pollution and bladder cancer
301 incidence in general population, we conducted analyses in a large pooled cohort within the Effects of
302 Low-Level Air Pollution: A Study in Europe (ELAPSE) project (16). ELAPSE builds on the ESCAPE
303 collaboration by pooling data from selected cohorts and extending the follow-up period. In addition,
304 we strengthened exposure assessment which allowed better coverage of included cohorts in ELAPSE.
305 In the present study, we assessed the associations between bladder cancer incidence and long-term
306 exposure to PM_{2.5}, NO₂, BC and O₃. We further explored potential bladder cancer risks with specific
307 elemental components in PM_{2.5}, in an attempt to identify the most responsible air pollution sources.

308

309 **2. Methods**

310 2.1 Study population

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

325 2.2 Exposure assessment

326 We investigated exposure to PM_{2.5}, NO₂, BC, warm season O₃ (hereafter referred to as O₃) and eight *a*
327 *priori* selected PM_{2.5} elemental components in the present study. The eight components were selected
328 in the ESCAPE study to represent major pollution sources in Europe: copper (Cu), iron (Fe) representing
329 non-tailpipe traffic emissions; zinc (Zn) representing industrial emissions primarily; sulfur (S)
330 representing long-range transport of secondary inorganic aerosols; nickel (Ni) and vanadium (V)
331 representing mixed oil burning/industry; silicon (Si) representing crustal material; and potassium (K)
332 representing biomass burning (28, 29).

333 We assessed 2010 annual average air pollution exposures with Europe-wide hybrid LUR models (30,
334 31), which incorporated ground-based measurements, satellite-derived estimates, chemical transport
335 model estimates, land-use, road and population density data. The modeling of PM_{2.5}, NO₂ and O₃
336 exposures was based on the European Environmental Agency AirBase routine monitoring data (30),
337 whereas the modeling of BC (30) and elemental composition exposures (31) was based on the
338 standardized ESCAPE monitoring data. The hybrid LUR models were developed using supervised linear
339 regression (SLR) and validated with five-fold hold-out validation. The models explained a moderate to
340 large fraction of the measured concentration variation at the European scale (i.e., 66% for PM_{2.5}, 58%
341 for NO₂, 51% for BC, 60% for O₃ and 41% to 79% across elemental components). Exposure models for
342 PM_{2.5} elemental composition were also developed with the Random Forest (RF) algorithm. The RF
343 models consistently outperformed the SLR models at the European scale, whereas the SLR and RF
344 models explained within-area variability similarly (31). In the present study, we primarily exploited
345 within-cohort exposure contrasts and thus interpreted the SLR and RF models equally. The exposure
346 models were applied to create 100 x 100 m grids of the predicted air pollution concentrations covering
347 the entire study area. Exposure to air pollution was assigned to participants' baseline residential
348 addresses. We truncated negative elemental composition exposure predictions to zero, and a few
349 unrealistically high exposure predictions to a maximum modeled concentration for each element (31).
350 Truncation was performed for SLR-modeled exposures (mostly to negative predictions): 12.9% for Cu,
351 0.6% for Fe, 14.1% for Ni, 16.8% for V and 3.4% for Zn. No truncation was needed for RF-modeled
352 exposures.

353 We selected 2010 as the primary year of exposure modelling because 2009-2010 was the period of
354 ESCAPE monitoring, which we used to develop BC and PM_{2.5} composition models (30, 31). For PM_{2.5},
355 this was the earliest year of a sufficiently wide coverage of PM_{2.5} monitoring across Europe (30). For
356 consistency, we used year 2010 for NO₂ and O₃ as well. This analysis assumes that the spatial contrast

357 of the relevant pollution concentrations remained reasonably stable from the baseline period (years
358 1985–2005, Table 1) to 2010 (30).

359 For PM_{2.5}, NO₂, BC and O₃, we also estimated exposures at each individual's baseline year using back-
360 extrapolation. Back-extrapolation was performed by using estimated concentrations from the Danish
361 Eulerian Hemispheric Model (DEHM) (32). DEHM modeled predictions of monthly average
362 concentrations across Europe at 26 x 26 km spatial resolution back to at least 1990 were obtained. We
363 compared temporal patterns of DEHM-modeled concentrations and ground-based measurements for
364 countries with monitoring data (30). To allow different spatial trends within Europe, we calculated
365 population weighted average concentrations at the Nomenclature of territorial units for statistics
366 (NUTS-1) spatial scale for application to the national cohorts. NUTS-1 reflects major socio-economic
367 regions (e.g., four regions in the Netherlands and 14 regions in France). For smaller study areas, we
368 calculated population weighted average concentrations within the study area. We back-extrapolated
369 concentrations using both a difference and a ratio method with 2010 as the baseline. With the
370 difference method, the concentration difference between a year and 2010 from the DEHM model is
371 added to all cohort exposures for that year. With the ratio method, the concentration ratio between
372 a year and 2010 from the DEHM model is used to multiply all cohort exposure for that year. We were
373 not able to estimate exposures to PM_{2.5} elemental components at baseline years, because we had
374 insufficient information on the elemental composition concentration in Europe over time.

375 2.3 Outcome

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

384 2.4 Statistical analyses

385 2.4.1 Main analyses

386 We applied Cox proportional hazards models to estimate associations between long-term air pollution
387 exposures and bladder cancer incidence, following the common ELAPSE analytical framework (33, 34).
388 In the Cox models, we stratified by subcohorts because the assumption of proportional hazards did
389 not hold for subcohorts. Using strata to account for between-cohort heterogeneity implies that we
390 mostly evaluate within-cohort exposure contrasts. Each air pollutant was included as a linear term in
391 the Cox models. Hazard ratios (HRs) and 95% CIs were calculated with a fixed increment for each
392 pollutant following the increments selected in previous ESCAPE and ELAPSE publications (17, 18, 35):
393 $PM_{2.5} - 5 \mu\text{g}/\text{m}^3$, $NO_2 - 10 \mu\text{g}/\text{m}^3$, $BC - 0.5 \cdot 10^{-5}/\text{m}$, $O_3 - 10 \mu\text{g}/\text{m}^3$, $PM_{2.5} \text{ Cu} - 5 \text{ ng}/\text{m}^3$, $PM_{2.5} \text{ Fe} - 100$
394 $\text{ ng}/\text{m}^3$, $PM_{2.5} \text{ K} - 50 \text{ ng}/\text{m}^3$, $PM_{2.5} \text{ Ni} - 1 \text{ ng}/\text{m}^3$, $PM_{2.5} \text{ S} - 200 \text{ ng}/\text{m}^3$, $PM_{2.5} \text{ Si} - 100 \text{ ng}/\text{m}^3$, $PM_{2.5} \text{ V} - 2$
395 $\text{ ng}/\text{m}^3$, $PM_{2.5} \text{ Zn} - 10 \text{ ng}/\text{m}^3$. Censoring occurred at the time of any cancer other than bladder cancer
396 diagnosis (except non-melanoma skin cancer), death, emigration, loss to follow-up or end of follow-
397 up, whichever came first. We specified three confounder models with increasing adjustment for
398 individual- and area-level covariates: Model 1 included age (as the time axis), subcohort (as strata),
399 sex (as strata), and year of enrollment (as a continuous variable); Model 2 further adjusted for
400 individual-level covariates, including marital status (married/cohabiting, divorced/separated, single,
401 widowed), smoking status (never, former, current), smoking duration (years of smoking) and smoking
402 intensity (cigarettes/day) for current smokers, squared smoking intensity, body mass index (BMI) in
403 categories (<18.5 , $18.5-24.9$, $25-29.9$, and $\geq 30 \text{ kg}/\text{m}^2$), and employment status (employed vs.
404 unemployed); Model 3 (main model) further adjusted for area-level mean income in 2001 (as a
405 continuous variable). The spatial scale of area varied from smaller neighborhoods and city districts
406 (CEANS, EPIC-NL, E3N) to municipalities (DCH, DNC, VHM&PP). Participants with missing exposure or
407 incomplete information on Model 3 covariates were excluded from all analyses to ensure
408 comparability among the model results.

409 Two-pollutant models were specified for all combinations of $PM_{2.5}$, NO_2 , BC and O_3 to assess the
410 robustness of effect estimates for one pollutant to inclusion of another. Two-pollutant models for
411 elemental composition were analyzed with $PM_{2.5}$ or NO_2 as the second pollutant. We adjusted for
412 $PM_{2.5}$ to investigate whether the association with individual elemental components remained after
413 adjustment for generic $PM_{2.5}$ mass (36); we adjusted for NO_2 in an attempt to disentangle the
414 individual component effect from traffic exhaust emission for which NO_2 is used as a marker.

415 2.4.2 Additional analyses

416 Given the fact that cancer development is usually a long process, the choice of the exposure period
417 may be critical and is often discussed in air pollution and cancer research (37). We therefore applied

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

428 We assessed the shape of the concentration-response functions (CRFs) for air pollution exposure and
429 bladder cancer incidence with natural cubic splines with three degrees of freedom. We performed
430 subset analyses for PM_{2.5}, NO₂, BC and O₃ exposures by restricting the main Model 3 analyses to
431 participants with exposure level below certain cut-off values.

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

436 For elemental composition, we performed analyses with exposures estimated with SLR and RF models
437 and interpreted results of the two exposure methods equally. We presented most elemental
438 composition analyses with the SLR-modeled exposures in the main text because PM_{2.5}, NO₂, BC and
439 O₃ exposures assigned to the cohorts were only estimated with SLR models (30). In a subsequent
440 analysis, we documented that, for PM_{2.5} and NO₂ separately, SLR and RF models performed similarly,
441 and had highly correlated predictions at randomly selected external validation sites (PM_{2.5}: Pearson r
442 = 0.89; NO₂: r = 0.93) (38). The SLR models are further more comparable to the LUR models used in
443 the ESCAPE study (10).

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

448

449 3. Results

450 After excluding 17.7% of the total population, the pooled study consisted of 302,493 individuals, of
451 whom 967 developed bladder cancers during 5,505,372 person-years of follow-up (Table 1). The
452 exclusions were due to fail in logical checks (e.g. date of death before date of cancer diagnosis; 0.9%),
453 cancer diagnosis before baseline (2.9%), missing exposure (0.5%), missing individual-level covariates
454 (12.5%) or area-level mean income (0.9%). Most of the cohorts started in the 1990s and had follow-
455 up until 2011–2015. The largest subcohort was VHM&PP, which contributed more than half of the
456 total person-years. Mean age of the participants at baseline ranged from 41.7 years to 72.5 years. Four
457 subcohorts included female participants only and the pooled cohort comprised 66% women. Current
458 smoker prevalence at baseline ranged from 13% to 37% with mean smoking duration ranging from
459 13.4 years to 43.2 years across subcohorts.

460 Figure 1 and Table S1 show the SLR-modeled air pollution exposure distribution in each subcohort.
461 The exposure concentrations were generally lower in the North European cohorts than in more
462 Southern cohorts. The within-cohort exposure contrast was substantial for NO₂, BC, Cu, Fe, Si and
463 more limited for PM_{2.5}, O₃, K, Ni, S, V and Zn. Exposure distribution for elemental composition
464 estimated with RF models is presented in Figure S1. We observed similar north-south concentration
465 gradient for RF-modeled exposures. For most elements, the within-cohort exposure contrasts were
466 smaller for RF- than SLR-modeled exposures. For PM_{2.5}, NO₂, BC and O₃, exposures back-extrapolated
467 to baseline years are shown in Figure S2. The baseline PM_{2.5} exposures were higher and more variable
468 than the 2010-exposure, whereas the baseline exposures to NO₂, BC and O₃ were similar or mildly
469 higher than the 2010-exposure.

470 In most subcohorts, exposure to PM_{2.5} was moderately correlated with exposure to BC and NO₂ (Table
471 S2). The correlations between NO₂ and BC were high in most subcohorts. O₃ exposures were negatively
472 correlated with PM_{2.5}, NO₂ or BC. Correlations of elemental composition with PM_{2.5} were mostly low
473 to moderate (Table S3). Correlations with NO₂ were mostly high for Cu and Fe in subcohorts (Table S4).
474 Correlations between air pollutants differed substantially in magnitude across cohorts, reflecting
475 differences in study area size and presence of major sources. We focused on within-cohort correlations
476 as the epidemiological analysis exploited mostly within-cohort exposure contrasts.

477

478 *Associations between air pollution and bladder cancer*

479 In the linear models, air pollution effect estimates were generally higher in the minimally adjusted
480 models (Model 1, Table S5). HRs were mildly attenuated after adjusting for individual-level covariates
481 (Model 2), and remained stable with further adjustment for area-level income (Model 3). The effect
482 estimates were generally similar in Model 1 and Model 2, comparing the population with complete
483 information on the corresponding model covariates and the population with complete data on Model
484 3 covariates, respectively, suggesting little selection bias was introduced by excluding participants with
485 missing covariates (Table S5). In the fully adjusted models, we observed a positive but statistically
486 nonsignificant association between PM_{2.5} exposure and bladder cancer incidence (Table 2). The HRs
487 for PM_{2.5} remained stable in two-pollutant models with adjustment for NO₂, BC or O₃, with wider CIs.
488 No association was evident for NO₂, BC or O₃. For elemental composition estimated with SLR models,
489 we observed positive associations for K, S, Si and Zn, which was only statistically significant for Zn
490 (Table 3). The HRs for K and Zn remained stable in two-pollutant models after adjusting for PM_{2.5} or
491 NO₂, with slightly wider CIs. The HRs for S and Si attenuated to unity after adjustment for PM_{2.5}. For
492 RF-modeled elemental composition, we observed similar patterns for HRs for K, S, Si and Zn, except
493 that HR for Si remained stable after adjusting for PM_{2.5} (Table S6). Effect estimates were larger for
494 elemental exposures estimated with RF models compared to SLR models, probably because of the
495 generally smaller exposure contrasts for RF predictions. In two-pollutant models with adjustment for
496 elemental composition, HRs for PM_{2.5} remained stable after adjusting for S or Si, whereas the HRs
497 attenuated after adjusting for K and Zn (Table S7). HRs for PM_{2.5} in two-pollutant models with Zn were
498 close to unity.

499 The sensitivity analyses did not alter the main findings. HRs for PM_{2.5} back-extrapolated to baseline
500 years attenuated mildly with narrower CIs compared to 2010 exposures (Table 4). The increased
501 precision in HR was especially evident for back-extrapolated exposure using ratio method, as the
502 exposure contrasts increased. For NO₂, BC and O₃, effect estimates with baseline exposure were
503 essentially unity. The effect estimates were stable with additional adjustment for smoking intensity
504 and duration in former smokers, education, occupational status and alcohol assumption in cohorts
505 that had such information (Table S8). The effect estimates were generally stable in analyses where we
506 excluded one cohort at a time (Figure S3). The 95% CIs widen after excluding the large VHM&PP cohort,
507 which contributed more than half of the person-years. For some pollutants, the HR point estimates
508 increased or decreased when dropping the VHM&PP with the 95% CIs including unity. The uncertainty
509 of HRs in most individual cohorts is large because of the small number of cases (Figure S4).

510 We generally observed a linear increase in the exposure-response function in the lower end of the
511 exposure distribution (Figure S5). For some pollutants, the CRFs showed a decreasing trend with wide
512 CIs at the end of the curve, where observations were few and shapes therefore were difficult to
513 interpret. A positive association was found at low levels of NO₂, decreasing at levels where the density
514 of data was still sizable, which was difficult to interpret. Subset analyses showed increased risks for
515 bladder cancer incidence when restricting to PM_{2.5} concentrations below 15 ug/m³ exposures with
516 wider CIs as the cancer cases became fewer (Table S9). For NO₂, positive associations were found when
517 excluding the highest NO₂ exposures, consistent with the CRF. There was no clear evidence for effect
518 modification by age group or smoking status. Effect estimates tended to be higher in participants with
519 baseline age < 65 y and current smokers, but the differences were not statistically significant (Table
520 S10). HRs for PM_{2.5} were significantly higher for male than female, which could be due to residual
521 confounding by smoking.

522 4. Discussions

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

528 Two previous cohort studies reported significantly positive associations between PM_{2.5} exposure
529 and bladder cancer mortality in the United States. Translating to a 5 µg/m³ increase in PM_{2.5} (the
530 exposure contrast used in our analyses), HRs of 1.15 (95% CI: 1.04–1.27) and 1.22 (95% CI: 1.00–
531 1.48) were reported in the ACS CPS-II and the NHIS studies (7, 8). We observed a lower HR (1.09,
532 95% CI: 0.93–1.27) for incident bladder cancer in the present study compared to the US studies. The
533 HRs for bladder cancer mortality and incidence may not be directly comparable because cancer
534 mortality reflects both disease incidence and survival following diagnosis. The 5-year survival rate
535 for people diagnosed with bladder cancer is relatively high (i.e., average of 77% for bladder cancer
536 cases diagnosed during 2010 through 2016 in the U.S.) (39). In a Hong Kong study where mortality
537 from both kidney and bladder cancers were evaluated together, a null association (HR: 0.98, 95% CI:
538 0.58–1.64 per 10 µg/m³ of PM_{2.5}) was reported (40). The Spanish Bladder Cancer Study reported an
539 OR of 1.06 (95% CI: 0.71–1.60) for the association between bladder cancer incidence and a 5.9 µg/m³
540 increase in PM_{2.5}, using a case-control study design (9). In the ESCAPE study, a negative association
541 with PM_{2.5} was reported with a wide CI (HR per 5 µg/m³ = 0.86, 95% CI: 0.63, 1.18)(10). We did not
542 attach too much importance to the negative point estimate given the wide CI. Built on the ESCAPE
543 cohorts, the present study observed a narrower CI for PM_{2.5} effect estimate, which may relate to
544 the longer follow-up and the conduct of a pooled analysis. The differences in effect estimates
545 reported in ESCAPE and ELAPSE could also be explained by the somewhat different cohorts included.
546 However, low heterogeneity across cohorts was observed in ESCAPE (10) and our results remained
547 stable in sensitivity analysis when dropping one cohort at a time. All of the above mentioned studies
548 adjusted for tobacco smoking in the statistical analyses, as smoking is the primary risk factor for
549 bladder cancer (41). There was no clear evidence of effect modification by smoking status in the
550 Spanish Bladder Cancer Study (9) and the ACS CPS-II (7), whereas the NHIS reported significantly
551 higher bladder cancer risks associated with PM_{2.5} among current smokers (8). We observed a
552 stronger though statistically non-significant association with PM_{2.5} among current smokers
553 compared to never smokers, suggesting there might be some residual confounding by smoking even

554 after adjustment for smoking status, duration and intensity in the present study. The small
555 difference in HRs between models adjusted for smoking and other lifestyle factors with age-sex
556 adjusted models, suggests confounding by smoking was likely limited.

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

570 In the present study, we found no evidence of associations between traffic-related air pollution and
571 bladder cancer incidence, reflected by effect estimates close to unity for proxies of tailpipe emission
572 (BC and NO₂) and non-tailpipe emission such as brake, tyre and road abrasions (Cu and Fe in PM_{2.5}).
573 We also did not find evidence that traffic-related air pollution was associated with lung cancer in
574 the same study (18, 34). Analyses in the Spanish Bladder cancer study, the ACS CPS-II and the ESCAPE
575 also showed no associations between NO₂ exposure and bladder cancer risks (7, 9, 10). The ESCAPE
576 further documented null associations with bladder cancer incidence for NO_x, BC, traffic density, and
577 Cu and Fe in PM (10). In an earlier study conducted in Amsterdam, no evidence for an association
578 between residential traffic density and bladder cancer incidence was found (13). In the DCH cohort,
579 which is a subcohort included in the current pooled analysis, a 100 ug/m³ increase in NO_x was
580 associated with an HR of 1.32 (95% CI: 0.80, 2.19) for bladder cancer incidence (11). Analyses in an
581 Israeli cohort of 9816 coronary intervention patients reported a similar magnitude of effect estimate
582 with a much wider CI for bladder cancer incidence: an HR of 1.07 (0.83, 1.37) per 10-ppb increase in
583 NO_x, translating to an HR of 1.40 (0.39, 4.83) per 100 ug/m³ increase in NO_x (12). We found positive
584 associations between NO₂ and bladder cancer incidence only at low concentrations, decreasing at

585 high NO₂ concentrations. The non-linear CRF was difficult to interpret and could be related to
586 competing risks for other diseases that were not accounted for in the present study.

587 We found robust associations between bladder cancer incidence and Zn exposure in the present
588 study. Zn was primarily related to industrial emissions in our exposure models, reflected by the large
589 proportion of variation in measurements explained by predictors representing industrial Zn
590 emission (31). The observed associations could be due to Zn exposures per se, or other correlated
591 components from industrial emissions. We did not observe consistently positive associations
592 between bladder cancer incidence and exposure to Ni or V in the present study, which were selected
593 to represent emission from mixed oil burning/industry (28, 29). Both Ni and V are suggested to
594 derived mainly from shipping emission in Europe (46), whereas Zn was considered as a source
595 identifier for metals industry (47). This is supported by ports from land-use being important
596 predictors for our Ni and V models (31). The correlations between Zn and Ni as well as Zn and V
597 exposures were low to moderate in the present study (average of cohort-specific Spearman
598 correlation coefficients ranged from 0.19 to 0.75)(17). The earlier Spanish Bladder Cancer Study
599 reported positive associations with bladder cancer for several indices of air pollution from industrial
600 emissions (14). The limitation of using exposure indices, such as proximity to industries, is that the
601 air pollution concentrations cannot be quantitatively estimated. In an analysis within population
602 residing in proximity of a coal-oil-fired thermal power plant in Italy, an increased risk of bladder
603 cancer was related to higher exposure to benzene and NO₂ in women aged ≥ 75 y (48).

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

614 One limitation is that the exposure assessments were based on 2010 measurements whereas most
615 included subcohorts started in the mid-1990s. We assumed that the spatial contrast of air pollution
616 remained stable over the past decades, which was confirmed by several studies in Europe for NO₂

617 (50-52), suggesting little bias was introduced. Importantly, we observed robust associations when
618 applying back-extrapolated exposures for PM_{2.5}, NO₂, BC and O₃. Unfortunately, we were not able
619 to assess associations with back-extrapolated exposures for PM_{2.5} elemental components because
620 of the insufficient information of trends over time. We cannot rule out the possibility that spatial
621 contrast for these air pollutants may have been less stable. Moreover, the generally moderate
622 performance of the elemental models may limit our ability to detect a potential association. As the
623 measurement errors introduced are likely nondifferential, the effect estimates are more likely to be
624 biased toward null. Another limitation is that we were unable to account for residential mobility
625 during follow-up and only have information on lifestyle factors at baseline, whereas the study
626 population may move or change their smoking and other habits over time. We further cannot rule
627 out the possibility of residual confounding by other missing covariates of potential interest, such as
628 occupational exposures. We, however, observed robust results in sensitivity analyses with
629 additional adjustment for occupational status or educational level in subsets of the pooled cohort.
630

631 **5. Conclusions**

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

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783

784 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	7,835	7,305 (93.2)	1992–1998	2011	15.3	21	47.0 ± 4.9	59	26	13.6 ± 7.4	27.8 ± 8.6
CEANS-SIXTY	4,180	3,660 (87.6)	1997–1999	2014	12.0	27	60.0 ± 0.0	50	21	13.3 ± 7.7	36.2 ± 10.1
CEANS-SALT	6,724	5,625 (83.7)	1998–2003	2011	9.9	26	57.3 ± 10.4	53	21	12.7 ± 8.1	37.6 ± 9.1
CEANS-SNACK	3,248	2,359 (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	8,769	7,430 (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

785 ^a The Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort (consisting four subcohorts: the *Stockholm Diabetes Prevention Program* (SDPP)(19), the
786 *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*
787 (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
788 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
789 *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
790 Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) is in Austria.

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

792 ^c For current smokers

793 Table 2. Associations between main air pollutants and bladder cancer incidence in single- and two-
 794 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)	-

795 Population size = 302,493; person-years at risk = 5,505,372; number of incident bladder cancer = 967; Hazard Ratio (95%
 796 confidence interval) presented for the following increments: PM_{2.5} – 5 µg/m³, NO₂ – 10 µg/m³, BC – 0.5*10⁻⁵/m, O₃ – 10
 797 µg/m³; main model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status,
 798 duration, intensity, intensity²), BMI, marital status, employment status and 2001 area-level mean income

799 ^a Two-pollutant models of BC and NO₂ are difficult to interpret because of high correlation (average of cohort-specific
 800 spearman correlation coefficients of 0.81) between BC and NO₂ (Table S2)
 801

802 Table 3. Associations between PM_{2.5} composition and bladder cancer incidence in single- and two-
 803 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)

804 Population size = 302,493; person-years at risk = 5,505,372; number of incident bladder cancer = 967; Hazard Ratio (95%
 805 confidence interval) presented for the following increments: PM_{2.5} Cu – 5 ng/m³, PM_{2.5} Fe – 100 ng/m³, PM_{2.5} K – 50
 806 ng/m³, PM_{2.5} Ni – 1 ng/m³, PM_{2.5} S – 200 ng/m³, PM_{2.5} Si – 100 ng/m³, PM_{2.5} V – 2 ng/m³, PM_{2.5} Zn – 10 ng/m³; main
 807 model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status, duration,
 808 intensity, intensity²), BMI, marital status, employment status and 2001 area-level mean income
 809 Exposures were estimated with supervised linear regression; effect estimates for elemental composition exposures
 810 estimated with random forest are shown in Table S6; Effect estimates for PM_{2.5} and NO₂ in two-pollutant models are
 811 shown in Table S7.

812 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)

813 Population size = 302,472; person-years at risk = 5,505,372; number of incident bladder cancer = 967; Hazard Ratio (95%
 814 confidence interval) presented for the following increments: PM_{2.5} – 5 µg/m³, NO₂ – 10 µg/m³, BC – 0.5*10⁻⁵/m, O₃ – 10
 815 µg/m³; main model adjusted for subcohort (strata), age (time axis), sex (strata), year of baseline visit, smoking (status,
 816 duration, intensity, intensity²), BMI, marital status, employment status and 2001 area-level mean income

817 ^a Exposure back-extrapolated to baseline years using ratio and difference methods respectively

818 Figure 1. Exposure distribution (corresponding values shown in Table S1)

819 The boundary of the box closest to zero indicates P25; furthest from zero – P75; bold vertical line inside the box – P50;

820 whiskers indicate P5 and P95

821 Subcohorts are shown from north to south

822 Exposures were estimated with supervised linear regression. Elemental composition exposure estimated with random

823 forest are shown in Figure S1.