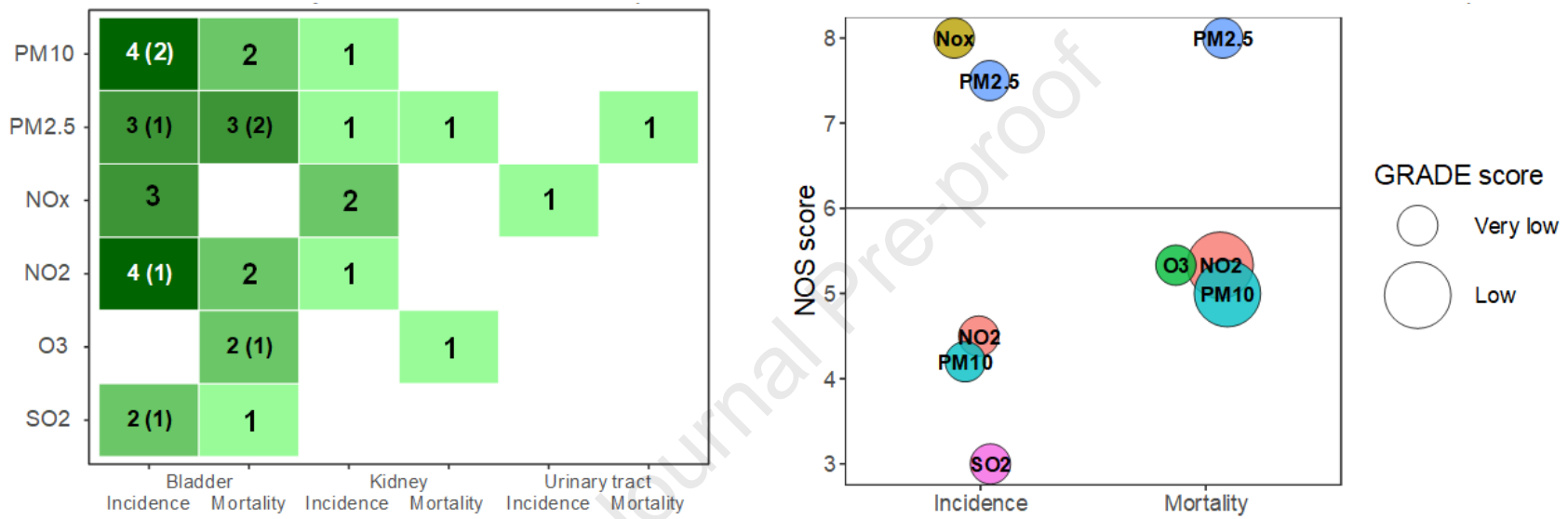
Evidence map of the association between urological cancer and air pollutants. The left panel shows the total number of studies (number of ecological studies between parentheses), color-coded based on number of available studies (from light green for 1 to dark green for 4). The right panel shows, for bladder cancer, the strength of the evidence assessed for each individual studies using the New-Castle Ottowa score (NOS) as y-axis (here we present the average of the NOS by pollutant and outcome, and the line depicts a NOS of 6, our cut-off to define good-quality articles), and for each pair of outcome-pollutant using the GRADE approach.



The results of this review showed a suggestive association between kidney and bladder cancer risk and air pollution, however the conclusions are based on few studies and most of them with a low GRADE score.

Air pollution exposure and bladder, kidney and urinary tract cancer risk: a systematic review

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Abstract

Background: Exposure to outdoor air pollution has been linked to lung cancer, and suspicion arose regarding bladder, kidney, and urinary tract cancer (urological cancers). However, most of evidence comes from occupational studies; therefore, little is known about the effect of exposure to air pollution on the risk of urological cancers in the general population.

Method: We systematically searched Medline, Scopus, and Web of Science for articles investigating the associations between long-term exposure to air pollution and the risk of urological cancer (incidence or mortality). We included articles using a specific air pollutant (PM_{10}, $PM_{2.5}$, …) or proxies (traffic, proximity index…). We assessed each study's quality with the Newcastle–Ottawa scale and rated the quality of the body of evidence for each pollutant-outcome with the GRADE approach. The different study methodologies regarding exposure or outcome prevented us to perform a meta-analysis.

Results: twenty articles (four case-control, nine cohort, and seven ecologic) met our inclusion criteria and were included in this review: eighteen reported bladder, six kidney, and two urinary tract. Modeling air pollutants was the most common exposure assessment method. Most of the included studies reported positive associations between air pollution and urological cancer risk. However, only a few reached statistical significance (e.g. for bladder cancer mortality, adjusted odds-ratio of 1.13 (1.03-1.23) for an increase of 4.4 µg.m-3 of $PM_{2.5}$). Most studies inadequately addressed confounding, and cohort studies had an insufficient follow-up.

Discussion: Overall, studies suggested positive (even though mostly non-significant) associations between air pollution exposure and bladder cancer mortality and kidney cancer incidence. We need more studies with better confounding control and longer follow-ups.

Keywords: Air pollution; Cancer; Mortality; Incidence; Systematic review

Introduction

Sixteen percent of the deaths from non-communicable diseases are attributed to air pollution(1). Exposure to ambient air pollution has been linked to several health outcomes, including incidence and mortality from cardiovascular, respiratory, and cancerous diseases(2-6). Respiratory and cardiovascular effects of air pollution exposure are well demonstrated in both occupational and the general population(7). Most of the available literature on the relationships between air pollution exposure and cancer focused on lung (8, 9) and child cancers(10, 11), and relied on occupational air pollution exposures(12, 13). In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as a human carcinogen, based on sufficient evidence especially on lung cancer. The IARC also suggested a positive association for bladder cancer(14). The link between outdoor air pollution exposure and bladder cancer was first reported at the end of the 19th century, based on the findings in a group of workers in the dye industry (15). Later occupational studies revealed that exposure to several air pollutants (such as polycyclic aromatic hydrocarbon (PAHs) and diesel engine exhausts) are linked with an increased risk for bladder cancer(16, 17). However, up to date, new evidence keeps coming out for the general population and other cancer sites including bladder(18-21), kidney(22, 23), and urinary tract(24, 25).

The likely shared mechanisms between air pollution and tobacco smoking -an established risk factor for bladder cancer- support the rationale for a link between bladder cancer and air pollution. Excretion of mutagenic metabolites of inhaled air pollutants through the urinary system could also increase the urological system

cells' exposure to carcinogens(26). However, the concentration of air pollutants in the general environment is considerably lower than in occupational settings, and little is known about the effect of general population exposure to air pollution on the risk of urological cancers.

In this review, we aimed to systematically review the available evidence on long-term exposure to air pollution, and surrogate indices of vehicle emissions, with the risk of bladder, kidney, and urinary tract cancers incidence and mortality.

Materials and Methods

Search strategy

This review was conducted according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines(27). We used three databases including Medline, Scopus, and Web of Science (without language restriction) to systematically search for the available literature on the association between long-term exposure to outdoor air pollution (and surrogate indices such as traffic proximity) and bladder, kidney or urinary tract cancer incidence and mortality published until the June 15th, 2019. Combination of MeSH and non-MeSH keywords related to outdoor air pollution as the exposure of interest: as exposure, particulate matters with an aerodynamic diameter smaller than 2.5 and 10 micrometers ($PM_{2.5}$ and PM_{10}), sulfur oxides and dioxide (SO_x and SO_2), nitrogen oxides and dioxide (NO_x and NO_2), ozone (O_3), carbon monoxide (CO), distance to road, traffic density, and, as the outcome, selected urological cancer incidence and mortality (kidney, bladder, urinary tract and “urinary cancer” in general) were used to search the selected databases (**Table** S1). We also conducted a manual search

from the reference lists of relevant original studies or reviews to identify any additional documents relevant for this review.

Study selection

After duplicates removal, titles and abstracts were evaluated according to the study inclusion and exclusion criteria by two independent reviewers (M.Z and E.L) (**Table** S2). The reviewers included all the studies that met these inclusion criteria and reported at least one association between the exposure to one of the air pollutants of interest (PM_{10}, $PM_{2.5}$, NO_2, NO_x, SO_2, O_3), or proxies of air pollution exposure, and one of the cancers of interest. In the case of inconsistency between reviewers, the third reviewer (B.J) assessed the eligibility criteria of the study, and then a consensual decision was taken by the three reviewers. Editorials, case reports, reviews, in-vitro, animal studies, as well as studies that reported exclusively the effects of occupational exposure, and indoor air pollutants were excluded. Due to the only recent development of exposure assessment models allowing estimating air pollution at the individual level, we also included studies that used proxies of air pollution exposure such as distance to major roads, traffic, or petrol station densities.

Data extraction

All relevant data including first author name (as the study ID), publication date, study title, location of study, study design, number of participants and cases, follow-up time (for cohort studies), population of interest, age group and sex of participants, exposure assessment method, type of air pollutant or proxy, type of outcome (mortality or incidence), type of cancer, outcome measurement method,

statistical method, type of observed exposure-response relationship (if reported), level of adjustment, the point estimate and 95% confidence intervals (CIs) of crude and adjusted effect size(s) were extracted in a Microsoft Excel sheet.

Quality assessment

Newcastle–Ottawa Scale (NOS):

The quality of each selected case-control and cohort study was assessed by the NOS, which was not applicable for ecologic studies (28, 29). The NOS is based on eight items distributed in three domains: (i) the selection of study groups, (ii) the comparability of cases and controls (or of exposed and non-exposed participants), and (iii) the ascertainment of exposure/outcome. Using a starring system, all items can earn one star, except the comparability item that can earn up to two stars (first, the studies were checked for adjustment for the minimal required set of *a priori* defined covariates (here we chose age, sex, occupation, and smoking) and second, they were checked for any further adjustment). The final NOS score of each study sums up the earned stars. We considered studies with exposure assessment via land-use regression or dispersion models linked to residential addresses as a gold standard and highest exposure assessment quality. For cohort studies, a minimum of 10 years was considered a sufficient follow-up time. As we found no universally accepted criterion for the definition of good-quality based on the NOS score, we considered a cut-off score of 6 out of 9 to define good-quality articles. We finally reported the mean NOS score according to the study design and cancer site.

Grading of Recommendations Assessment, Development, and Evaluation system (GRADE):

We evaluated the overall quality of the evidence using the GRADE system for each pair of exposure-outcome(30). GRADE is a subjective framework yielding a score between “high”, “moderate”, “low”, and “very low”. GRADE starts the evaluation by attributing a score from the study design and then uses eight domains to modify this score. GRADE was initially developed for clinical practice recommendations, for which observational studies were considered low-quality. Yet in air pollution epidemiology, nearly all studies are observational; therefore, we adapted the original methodology as follows. As a starting point, we considered the cohort and case-control studies as the sources with high-quality evidence, and cross-sectional and ecologic design studies as sources with low-quality evidence. The original score can upgrade/downgrade according to five downgrading (risk of bias, inconsistency, imprecision, indirectness, and publication bias) and three upgrading domains (dose-response trend, the magnitude of associations, and residual confounding). For the risk of bias, representativeness of population, the origin of controls, inadequate control of confounders, and inadequate follow-up (ten years) were considered. More specifically for the control of confounders, adjustment for major known risk factors of the urinary system cancers such as sex, occupation, age, and smoking was considered necessary to study the possible effect of air pollution. Indeed bladder and kidney cancers are known smoking-related (31-33), and an important proportion of bladder cancer is attributed to occupational exposures(12). Heterogeneity in the effect sizes and non-overlapping of reported confidence intervals were considered as the measures of inconsistency. Imprecision was considered as a small number of studies (less than three) or studies showing associations in the opposite direction for the same pair of exposure/outcome. The accordance of the population, exposure, and outcome of the studies to the targeted population, exposure, and outcome of this review was considered as a measure of indirectness. In this review, deciding about publication

bias was hard due to the impossibility to perform a meta-analysis and lack of funnel plot or relevant statistical tests. Therefore, we could just consider the omission of reporting certain results in the included papers as possible publication bias. Reporting of an effect size above 1.4 (based on the estimates reported in studies on air pollution and cancer) or of a dose-response relationship, as well as the role of residual confounding, were also considered for upgrading. We considered only one type of residual confounding: cases where the exposure misclassification could shift the association towards the null.

Statistical methods used in the included papers

Studies reported results of associations (crude and/or adjusted) by odds ratio (OR), relative risk (RR), the hazard ratio (HR), incidence rate ratio (IRR), or standardized incidence ratio (SIR), and their corresponding CIs. Because of the diversity of outcomes, air pollutants, and study designs, each exposure-outcome pair included at most four articles, and often with different statistical models and measures of association; therefore, we were unable to perform a meta-analysis. Instead, we reported the quantitative outcomes for those exposure-outcome associations that were available in more than one study in a separate table for each site of cancer.

Results

General characteristics of studies

A total of 2773 items were identified through databases searches (we did not find any non-English paper). We did not find any other articles using other sources. After duplicate removal, we screened titles and abstracts and selected 70 articles

for full-text evaluation; we excluded 50 articles because they did not meet the inclusion criteria. We found four case-control studies(18-21), nine cohort studies(22-24, 34-39), and seven ecologic studies(25, 40-45), totalizing 20 articles included into this review (**Figure 1, Table 1 and Table 2**). All of these studies were conducted since 2004, and since 2010 for 85% (n=17) of them (19, 20, 22-25, 34, 35, 37-45). Nine studies took place in Asia(20, 21, 24, 39-42, 44, 45), nine in Europe(18, 19, 22, 23, 25, 34-37) and two in North America(38, 43). Five of the Asian studies were ecologic(40-42, 44, 45), with two case-control studies (20, 21) and two cohort studies (24, 39). European studies included one ecologic study(25), two case-control studies (18, 19), and six cohort studies(22, 23, 34-37). In the case-control studies, the number of cases ranged between 680(21) and 1641(20) (sum of cases across all case-control studies: 4478). In the cohort studies, the number of outcomes ranged between 73(22) and 1324(38), with total of 5438 cases across all cohorts.

Quality assessment

Tables 3 and 4 and Figure 2 report quality scores of the selected cohort and case-control studies respectively (as stated in the methods section, the NOS was not applicable for ecologic studies). Pooling all relevant articles, we estimated an average NOS score of 6.58, which is higher than our cut-off of six which defines good-quality.

The seven cohort studies on bladder cancer earned between 3 and 9 stars and five of them earned a NOS score of six or higher. Exposure and outcome assessment domain was the strongest domain across studies, whereas the adequacy of follow-up and comparability (in terms of the adequacy of adjustment for confounders) was the weakest domain. The four case-control studies on bladder cancer earned

between four and six stars (only one study earned six stars). The strongest items in the case-control studies were using the same method of exposure assessment and ascertainment for both cases and controls across studies and also control selection. None of the case-control studies reported a response rate.

The four cohort studies on kidney cancer all earned at least 6 stars (mean NOS score: 7.75), and the two cohort studies on urinary tract cancers earned 7 and 9 stars: they were considered of good-quality with the same weak points as the cohort studies on bladder cancer (follow-up inadequacy and lack of comparability).

GRADE assessment

The GRADE approach was used to assess the overall quality of the evidence of the nine exposure-outcome pairs that were investigated by two or more studies (all were on bladder cancer risk) (**Table S3- S11**). In most cases, the level of evidence was very low, except for "PM_{10} and bladder cancer mortality" and "NO_2 and bladder cancer mortality" (**Figure 2**). The most frequent limitation concerned "indirectness" due to the few numbers of studies for each pair, especially $PM_{2.5}$ and bladder cancer mortality. The risk of bias was quite high, due to insufficient follow-up time, unclear case definition, imprecise exposure assessment, lack of representativeness, and residual confounding, decreasing the score on the quality of evidence for all exposure-outcome pairs except for bladder cancer incidence and $PM_{2.5}$. The available evidence for bladder cancer mortality and exposure to NO_2 or PM_{10} was consistent. However, for the other exposure-outcome pairs, we downgraded the evidence quality because of inconsistency. The magnitude of the reported effect size was generally lower than 1.4 (except for NO_2 and PM_{10} with bladder cancer mortality). The lack of sufficient evidence of a dose-response relationship prevented us from upgrading the score in this domain. Potential

exposure misclassification (as a measure of residual confounding in this review) was observed for all reported exposure-outcome pairs, except NOx exposure and bladder cancer incidence.

Exposure assessment

Different air pollutants or proxies of air pollution with different quantification approaches were used across the studies (**Table 1 and 2; Figure 2**). Among classic air pollutants, studies reported results for PM_{10}(21-23, 25, 34, 35, 42), $PM_{2.5}$(19, 23, 35, 38, 39, 44, 45), $PM_{2.5}$ absorbance(23, 35), organic carbon in PMs (23, 35), and elemental composition of PMs (23, 35); and for gases NO_x(24, 35, 37), NO_2(19, 21, 23, 34, 35, 38, 40), SO_x(22), SO_2(21, 34, 42), hydrogen sulfide (22), O_3(21, 38), CO(21), and benzene (34). NO_2, $PM_{2.5,}$ and PM_{10} were the most used air pollutants across studies (each one reported in seven studies).

Air pollution modeling was the most common method of exposure assessment in the selected studies, whether by dispersion modeling(22, 25, 34), land-use regression(19, 23, 24, 35, 37-39), remote sensing(40, 45), interpolation(42) and kriging(44). One study used stationary stations measurements of criteria air pollutants at the municipality level(21). Seven studies also reported results for proxies of air pollution such as traffic density, presence of major roads near residential addresses(19, 23, 35, 36), window facing traffic(18, 19), type and quantity of traffic, petrol station density near the residential area(20), and annual total waste gas emission at the state level(41). The exposure assessment method was unclear in one study(43).

Reported outcomes

We considered cancer incidence or mortality separately. Different approaches were used across studies to assess the outcome. Most of the studies used data from national or regional cancer registries(23-25, 34-37, 40-45), however, two case-control studies used data from hospital registries(18, 19), and five others used death certificates(20-22, 38, 39). Hereafter, we will summarize the evidence on each cancer site (bladder, kidney, and urinary tract), first regarding incidence and then mortality.

Bladder cancer

Eighteen studies reported bladder cancer incidence and/or mortality data (**Table 1**), including seven cohort studies (22, 24, 34-38) with total cancer cases of 3219, four case-control studies with a total of 4478 cases (18-21), and seven ecologic studies (25, 40-45). Five of the cohort studies(24, 34-37), two of the case-control studies (18, 19), and five of the ecologic studies(25, 40-42, 45) dealt with bladder cancer incidence; six (20-22, 38, 43, 44) (including two cohorts(22, 38), two case-controls(20, 21) and two ecologic studies(43, 44)) dealt with bladder cancer mortality.

Bladder cancer incidence

Among 26 associations (excluding correlation coefficients) on five air pollutants (excluding proxies), we found one null and six point-estimates below one, and all the other ones were above one (**Table** 5). But only three associations reached the statistical significance, for NO_2 (34) and $PM_{2.5}$(25). Unexpectedly, one of the cohort studies found a higher SIR in the areas with lower traffic intensity score compared to the areas with higher traffic intensity (SIR: 1.16 vs. 0.87)(36). The

two case-control studies(18, 19) – using the same epidemiologic data but different exposure measures ($PM_{2.5}$ and NO_2(19); and windows facing traffic and type and quantity of traffic(18))– found positive but not significant associations between exposures and bladder cancer incidence, and larger point estimates for non-smokers and women (but still statistically non-significant). In contrast to these cohorts and case-control studies, four ecologic studies(25, 40, 41, 45) found significant positive associations between at least one air pollution measure and bladder cancer incidence. However, the pollutants of interest in all these studies were different and it was impossible to compare the results.

Bladder cancer mortality

Among 17 associations on five air pollutants and bladder cancer mortality from non-ecological studies, only one point-estimate was below one, the others were positive (with generally higher point-estimates than for bladder cancer incidence) and actually, six reached statistical significance(21, 25, 38). Further, Liu *et al.* (2009) found significant *p* for trends across tertiles of exposure for NO_2, SO_2, and PM_{10} – although in unadjusted models. When using a pollution index (combining NO_2 and SO_2), they also found a significant p for trend. When analyzing associations in subgroups of the population, Ancona *et al.* (22) found a positive and significant association between bladder cancer mortality and hydrogen sulfide exposure in women (HR=1.35; 95% CI: 1.00–1.82); Turner et al (38) reported a significant association with $PM_{2.5}$ only for men, never smokers and those with at least high school education. In Taiwan(20, 21), the case-control studies found a significant positive association between the days with ozone pollution (as a measure of short-term exposure to air pollution) and bladder cancer mortality(21),

but no association with the density of petrol stations near the residential addresses (20).

Three ecologic studies reported inconsistent results for $PM_{2.5}$: a non-significant association(43), a significantly positive association(44), and a significantly negative association(45). Smith *et al.* also found a significant association between bladder cancer mortality and ozone days(43).

Kidney cancer

Five studies - including four cohorts (22, 23, 37, 38) and one ecologic study(41) - reported associations between kidney cancer and air pollution (**Table 2**). Two studies(22, 38) dealt with kidney cancer mortality and three (23, 37, 41) with kidney cancer incidence. The two cohort studies(23, 37) on kidney cancer incidence included 792 cases. For kidney cancer mortality, the largest study was from "the Cancer Prevention Study-II" with 927 cases (38). Another study was based on the data from 14 European cohorts of the ESCAPE study with 697 kidney cancer incidence cases(23).

Kidney cancer incidence

The five associations between kidney cancer incidence and three air pollutants were all positive but none reached statistical significance(37, 46). One of the two studies investigating NOx reported a point estimate larger than 1.4 (**Table 6**). The study pooling 14 European cohorts (23) reported heterogeneous findings across cohorts. The ecological study reported a significant positive correlation between waste gas emissions and kidney cancer incidence; the analyses by sex indicted

significant correlations for both men and women with a coefficient of 0.8 for male – twice as high as for women (41).

Kidney cancer mortality

The two cohort studies on air pollution and kidney cancer mortality (22, 38) did not investigate the same air pollutant. Turner *et al.* (38) found a significant association with $PM_{2.5}$ (HR= 1.14; 95% CI:1.03-1.27), but not for NO_2 or O_3. The analyses on subgroups showed that this association was only significant among men and current smokers. Ancona *et al.* (22) found no significant association between kidney cancer mortality and NO_2, PM_{10}, hydrogen sulfide or SO_X exposure.

Urinary tract cancer

Two cohort studies reported associations between air pollution exposure and urinary tract cancer incidence(24) and mortality(39) (**Table 2**). Both studies found non-significant associations between these outcomes and exposure to selected air pollutants.

Discussion

In this study, we reviewed the available body of evidence on the association between the bladder, kidney, and urinary tract cancers incidence and mortality and

air pollution exposure, concluding to *a suggestive association between kidney and bladder cancer risk and air pollution*.

Indeed, overall five cohorts found small to moderate positive associations especially for bladder and kidney cancer mortality (even mostly non-significant) with different air pollutants exposure. Five out of seven ecological studies found a significant increase in the risk of bladder and kidney cancer incidence and mortality. Evidence on the association between air pollution exposure and kidney cancer seems stronger compared to bladder cancer, as we found proportionally more papers with positive and significant associations even if based on only three studies. Additionally, for bladder cancer, the results on mortality were more suggestive than on incidence. Most of the studies included had an acceptable quality in terms of NOS score, and the weakest point was generally low quality in adjustment and insufficient follow-up time (in the case of cohort studies). In total, the quality of evidence on the associations between air pollutants and bladder cancer was very low or low. The use of different exposure indices, statistical approaches, effect sizes, outcomes, and study designs made it impossible to do a meta-analysis.

The currently available evidence on the association of bladder and kidney cancer incidence and mortality with air pollution exposure comes mostly from occupational environments concerning exposure to gasoline vapors(17), chlorinated solvents(47, 48), asbestos(49), pesticides(50) and PAHs (51). A review and meta-analysis found an increased risk of urinary bladder cancer in motor vehicle drivers, who were occupationally exposed to a considerable amount of traffic-related air pollution (52). However, even if the intensity of air pollution exposure in the general population is considerably lower than for the drivers and

industrial workers, considering lifetime exposure in the general population, it is reasonable to suppose that the exposure to air pollution could be associated with an increased risk of urinary tract cancers. Several mechanisms could explain the relationship between exposure to air pollution and urological cancer. For instance, recent animal studies have shown that exposure to $PM_{2.5}$ can induce angiotensin/bradykinin system imbalance, subsequent early kidney damage and oxidative stress, and/or inflammation, which finally can cause cancer(53). A glomerular filtration rate reduction was also associated to exposure to particulate matters in those living near a major roadway(54) and also in those exposed to particulate matter(55); this reduced glomerular filtration rate could be a predictor of kidney and bladder cancer recurrence and progression(56, 57). These physiological findings suggest that exposure to air pollutants could induce lesions on the urinary system ultimately leading to urological cancers.

One of the main weaknesses of the non-ecological included studies was an inadequate adjustment for confounders. In addition to the main confounding variables described above, several studies have reported an association between environmental tobacco smoke (passive smoking) and kidney(58) and bladder cancer(59, 60). Not only not all of the selected papers in our review adjusted their analyses for smoking status, but none of them considered passive smoking exposure. Additionally, ecological studies could not include these variables in their models because of their natural design limitations. The other main weakness of the non-ecological studies was that they did not consider an adequate follow-up time. In addition, another major issue concerns the air pollution exposure assessment: since cancer occurrence is a chronic process, and since the spatial patterns of the environmental stressors may change over the years as well as studies' participants may move, taking a unique exposure value in the analyses may lead to exposure

misclassification. Considering that for the long-term exposure there is more spatial than temporal variability, taking one value as an exposure poses a problem especially for people moving over time(61). Most of the selected studies do not include information on historic exposures at the individual level. Another important yet seldom addressed the question in the available literature is how long the latency period between air pollution exposure and cancer outcomes should be considered in the statistical analyses. Therefore, because the selected studies used air pollutant exposures that do not necessarily take into account the long latency period between exposure and occurrence of outcomes, the co-occurrence of several environmental exposures, and the historic exposures, their analyses may yield biased risk estimates.

Other limitations of the included studies are the following. Ambient air pollution and noise usually co-occur in the environment(62). Recent studies suggest a possible association between noise exposure and cancer(63, 64). Considering noise exposure, the existence or type of insulation, and opening or closing pattern of windows or time-activity patterns of participants in future studies is advisable. Additionally, the inclusion of the role of indoor air pollution is also worthwhile. Castaño *et al.* (18) found that living more than 40 years in a city with a population of more than 100,000 was associated with an increased risk for bladder cancer. Exposure to air pollution could be an underlying cause of the urban-rural difference in cancer incidence and mortality. However, other factors such as a different lifestyle and different environmental exposures in rural and urban areas (such as higher noise, or light at night exposures and lower green space access for urban-dwellers) should not be neglected. All of these factors are correlated and could be regarded as underlying factors in the etiology of the cancers.

Different measures of air pollution exposure were reported in the studies selected in this review. Two studies based on the same epidemiologic data, but using either direct air pollution measures or proxies to assess exposure, found similar results: this indicates the comparability of this two exposure assessment approaches. Traffic indicators seem to be a good alternative in the case of data paucity to predict long-term exposure to air pollutants(65). However, proximity models may lead to greater misclassification than models based on direct air pollution measurements, such as land use regression (66). Both approaches are based on the residential addresses of the participants, and relying only on residential addresses can increase the risk of non-differential misclassification. Without knowing the activity pattern of the participants, such as commuting to the workplace, it is not possible to know their precise exposure. Additionally, relying on self-report, as noticed in some studies(18), could introduce further bias. Given the availability of modeling data on air pollutants or traffic measures, the limiting step in the ecologic studies is the spatial resolution of outcome data instead of exposure. For example, in most studies, the exposure data are available in finer resolution (several kilometers'), compared to the outcomes (mostly reported in the level of the region or district).

Strengths and limitations

To our knowledge, this is the first systematic review on the association between air pollution exposure in the general population and bladder, kidney, and urinary tract cancer incidence and mortality. We found only one review on the associations between exposure to particulate matters and urological cancers in the general

population (67). However, it was not a systematic but narrative review, which focused only on PM. Moreover, more than half of the studies included in our review have been published between 2015 and 2019, whereas the previous one included articles up to 2017: therefore an updated review of the evidence seemed useful necessary. In this review, we collected evidence from all types of study design and using different direct and indirect air pollution exposure metrics. Another strength of our review is that we encompassed both incidence and mortality evidence, which could give a broader insight into the possible associations between air pollution and urologic cancer. Using a strict quality assessment tool made it possible to compare the quality of the studies. However, our study suffers from several limitations. First of all, due to huge heterogeneity in the exposure metrics, study design, type of outcomes, and cancers and reported effect sizes, it was impossible to do a meta-analysis. We also were unable to detect publication bias in our study objectively. Additionally, nearly one-third of the selected studies were ecologic in design, and we were unaware of the standard and applicable instrument to measure and rank the quality across ecologic studies.

Conclusion

The results of this review showed a suggestive association between kidney and bladder cancer risk and air pollution. However, the diversity of outcomes, air pollutants, and study designs prevented us to conduct a meta-analysis, and furthermore, we identified several major shortcomings in many studies. Therefore, the results of our review could be used in the conduction and design of future studies for the assessment of the associations between ambient air pollution and cancer especially bladder and kidney cancer. Future studies should consider a

more comprehensive adjustment, and more accurate exposure assessment and ascertainment methods.

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Role of the funding source

The study funder did not contribute to the study design, data collection, data analysis, data interpretation, or writing of this manuscript. The corresponding author had full access to all the data used in this study and had final responsibility for the decision to submit for publication.

Contributors

MZ, EL, and BJ contributed to the study design. MZ and EL did the evidence screening. BJ contributed to the selection of papers with no-consensus by MZ and EL. MZ took the lead in drafting the manuscript. All authors contributed to the interpretation of data, provided critical revisions to the manuscript, and approved the final draft.

Declaration of Competing Interest

We declare no competing interest.

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List of Figures

Figure 1. PRISMA flow diagram for the systematic review of the association between air pollution exposure and the risk of selected urological cancers.

Figure 2. Evidence map of the association between urological cancer and air pollutants. The left panel shows the total number of studies (number of ecological studies between parentheses), color-coded based on the number of available studies (from light green for 1 to dark green for 4). The right panel shows, for bladder cancer, the strength of the evidence assessed for each studies using the NOS score as y-axis (here we present the average of the NOS score by pollutant and outcome, and the line depicts a NOS score of 6, our cut-off to define good-quality articles), and for each pair of outcome-pollutant using the GRADE approach.

List of Tables

Table 1. Summary of finding for the association between exposure to air pollution and bladder cancer risk

Table 2. Summary of finding for the association between exposure to air pollution and kidney and urinary system cancer risk

Table 3. Newcastle-Ottawa Scale (NOS) score for the cohort studies on the association between air pollution exposure and bladder, kidney, and urinary cancer risk

Table 4. Newcastle-Ottawa Scale (NOS) score for the case-control studies on the association between air pollution exposure and bladder, kidney, and urinary cancer risk

Table 5. Reported associations between exposure to outdoor air pollution exposure and bladder cancer risk

Table 6. Reported associations between exposure to outdoor air pollution exposure and kidney and urinary cancer risk

List of supplement Tables

Table S1. The sample search algorithm used for literature search on outdoor air pollution exposure (as an exposure) and selected urological cancer incidence and/or mortality (as an outcome) on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Last updated on June 15, 2019.

Table S2. Inclusion and exclusion criteria based on PECOS (population, exposure, comparison, outcome and study type) for a systematic review on the association between outdoor air pollution exposure and risk of selected urological cancers

Table S3: GRADE assessment for the association between exposure to PM_{10} and risk of bladder cancer incidence

Table S4: GRADE assessment for the association between exposure to PM_{10} and bladder cancer mortality

Table S5: GRADE assessment for the association between exposure to $PM_{2.5}$ and risk of bladder cancer incidence

Table S6: GRADE assessment for the association between exposure to $PM_{2.5}$ and bladder cancer mortality

Table S7: GRADE assessment for the association between exposure to NO_2 and risk of bladder cancer incidence

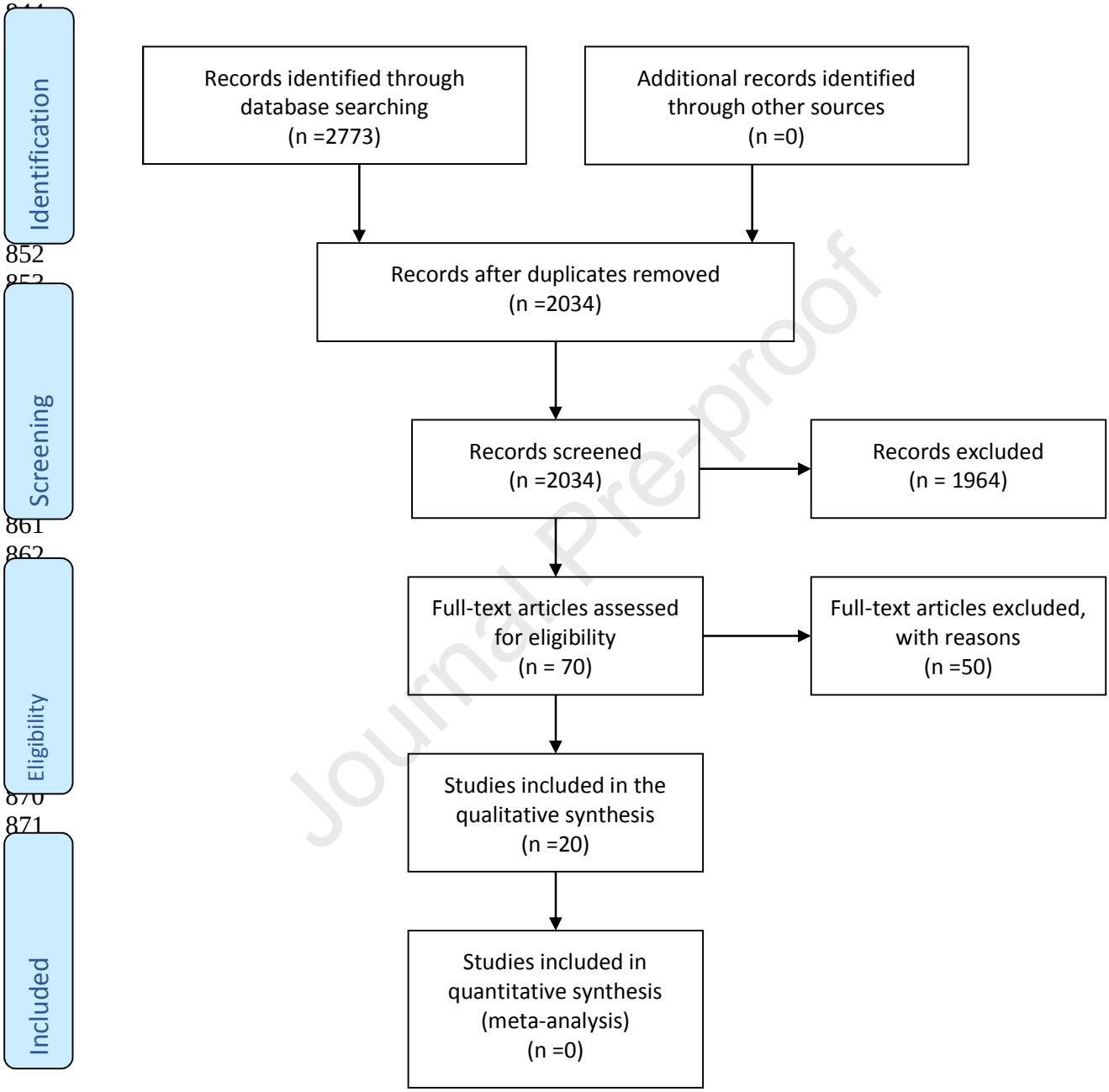
Table S8: GRADE assessment for the association between exposure to NO_2 and risk of bladder cancer mortality

Table S9: GRADE assessment for the association between exposure to NO_x and risk of bladder cancer incidence

Table S10: GRADE assessment for the association between exposure to SO_2 and risk of bladder cancer incidence

Table S11: GRADE assessment for the association between exposure to O_3 and risk of bladder cancer mortality

Figure 1. PRISMA flow diagram for the systematic review on the association between air pollution exposure and the risk of selected urological cancers.



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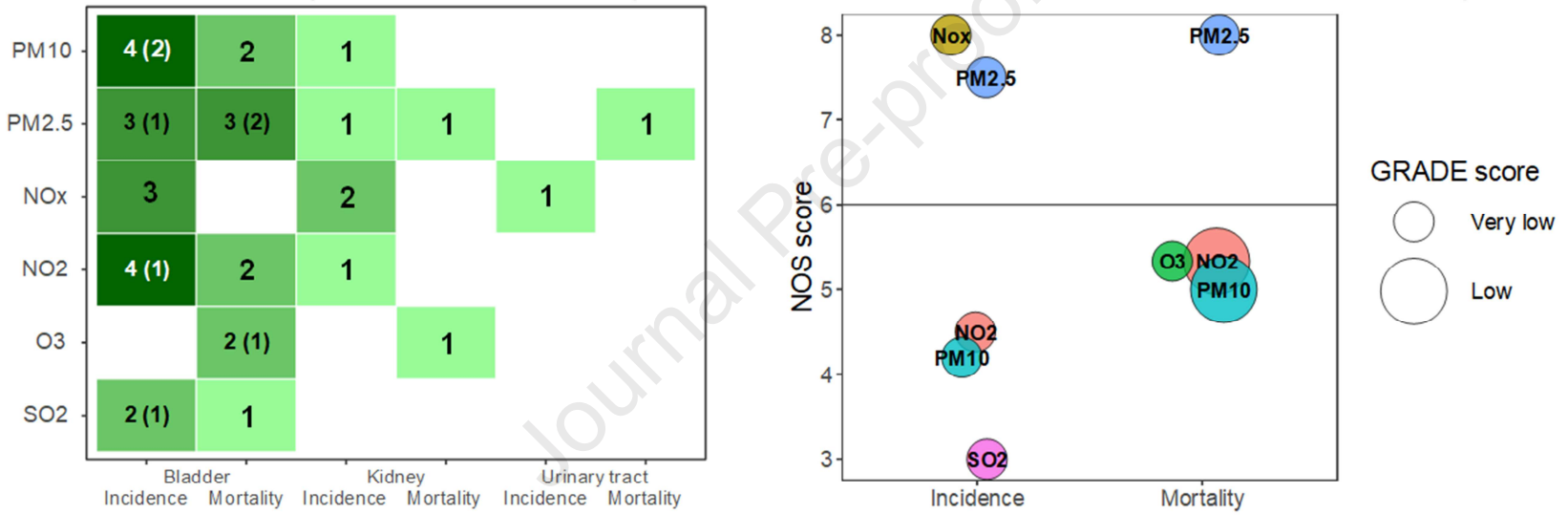

882 **Table 1. Summary of findings for the association between exposure to air pollution and bladder cancer risk**

First author(year); study location‡	Design; number of cases/outcomes	Case definition	Exposure assessment and metrics	Adjustment	Findings
Turner et al. (2019); Spain	Case-control (case: 938)	Incidence (histologically confirmed hospital cases)	LUR ($PM_{2.5}$; NO_2); windows facing a street with traffic (including number of traffic lanes and traffic intensity)	Age group, sex, region, smoking, high-risk occupations	No clear association either for ambient $PM_{2.5}$ or NO_2. No evidence for a trend.
Wang et al. (2019); China	Ecologic study	Incidence and mortality (cancer registry and mortality data)	Remote sensing ($PM_{2.5}$)	Unclear	A positive association between $PM_{2.5}$ exposure and bladder cancer incidence, but a negative association for bladder cancer mortality.
Cong et al. (2018); China	Ecologic study	Incidence (cancer registry)	Annual waste gas emissions (total volume of waste gas, industrial waste gas, other waste gas, SO_2, and soot)	Sex, number of doctors per 10,000 population, education, Engel's coefficient	A significant association for annual waste gas emission and bladder cancer incidence trend. The gender-specific analysis was only significant for men.
Cohen et al. (2018); Israel	Cohort (outcome: 74)	Incidence (cancer registry)	LUR (NO_X)	Sex, smoking, neighborhood socioeconomic status, ethnicity, hypertension, diabetes, chronic heart and renal failure, hemoglobin levels	A non-significant and small positive association was found. The effect size did not change after adjustment.
Collarile et al. (2017); Italy	Cohort (outcome: 650)	Incidence (cancer registry)	Dispersion model (C_6H_6, NO_2, PM_{10}, SO_2)	Unclear	Only in women aged 75 years or older the risk increased by increasing exposure to benzene and NO_2. The associations for PM_{10} or SO_2 were not linear.
Radespiel-Troger et al. (2017); Germany	Ecologic study	Incidence (Cancer registry)	Dispersion model (PM_{10})	Age, deprivation, age-adjusted lung cancer and chronic liver disease mortality rate	A significant positive association between PM_{10} exposure and bladder cancer in both sexes. The relative risk in males was lower than females.
Pedersen et al.	15 prospective cohort (outcome: 943)	Incidence (cancer registry)	LUR (PM_{10}; $PM_{2.5}$; $PM_{2.5}$ absorbance; NO_2; NO_x;	Age, sex, calendar time; smoking, occupation, employment,	No association.

First author(year); study location‡	Design; number of cases/outcomes	Case definition	Exposure assessment and metrics	Adjustment	Findings
(2016); Europe			traffic intensity on the nearest street; different PM elements; organic carbon in PM)	education; area-level socio-economic status	
Al-Ahmadi et al. (2013); Saudi Arabia	Ecologic study	Incidence (cancer registry)	Remote sensing (NO_2)	Unclear	A significant association for NO_2 in the ordinary least square regression model, but not in the geographically weighted regression model.
Raaschou-Nielsen et al. (2011); Europe	Cohort (outcome: 221)	Incidence (cancer registry)	LUR (NO_x), presence of a major road within 50 m	Smoking, education, occupation	A weak non-significant association for traffic-related air pollution and living near roads. Adjustment for potential confounders decreased the risk.
Eitan et al. (2010); Israel	Ecologic study	Incidence (cancer registry)	Spatially interpolated the monitoring data (SO_2; PM_{10})	Unclear	No increase in the risk neither for PM_{10} nor for SO_2.
Castano-Vinyals et al. (2008); Spain	Case-control (case:1219)	Incidence (histologically confirmed hospital cases)	Proximity to industries, windows facing traffic, size of the city of residence, type and quantity of traffic	Age, sex, region, smoking, occupation, consumption of fruits and vegetables; exposure to disinfection by-products in water	No association for having windows facing a street with traffic, number of traffic lanes, traffic intensity, or living in proximity to industry. Associations were stronger among non-smokers and women (non-significant difference).
Visser et al. (2004); The Netherland	Cohort (outcome: 151)	Incidence (cancer registry)	Daily traffic intensity score	Unclear	The standardized incidence rate in areas with lower traffic intensity score was higher.
Turner et al. (2017); USA	Cohort (outcome:1324)	Mortality (cause of death from a questionnaire)	LUR ($PM_{2.5}$; NO_2; O_3)	Age, gender, race, education, marital status; BMI; smoking, dietary intake, consumption of alcoholic beverages; occupational exposures	Significant positive associations for $PM_{2.5}$ and NO_2 in minimally and fully adjusted models. It was non-significant for O_3. $PM_{2.5}$. Results were only significant for men, never smokers, and those with at least high school education.

First author(year); study location‡	Design; number of cases/outcomes	Case definition	Exposure assessment and metrics	Adjustment	Findings
Yeh et al. (2017); Taiwan	Ecologic study	Mortality (data source was unclear)	Kriging ($PM_{2.5}$)	Unclear	In both sexes, $PM_{2.5}$ was significantly associated with bladder cancer mortality.
Ancona et al. (2015); Italy	Cohort (outcome: 73)	Mortality (death registration system)	Dispersion modeling (PM_{10}; H_2S; SO_X)	Sex, age, education, occupation, civil status, area-based SEP index, outdoor NO_2	H_2S exposure was significantly associated with bladder cancer mortality in women. No other significant associations were found.
Smith et al. (2015); USA	Ecologic study	Mortality (cancer registry)	Unclear ($PM_{2.5}$; O_3)	Unclear	Increase in bladder cancer mortality was associated with ozone days; but not with particulate matter air pollution days. On stratified analysis, the results were only significant for white male subjects.
Kung Ho et al. (2010); Taiwan	Case-control (case: 1641)	Mortality (death registration system)	Petrol station density	Marital status, urbanization	Higher risk for the groups with high levels of petrol station density in their residential municipality. No statistically significant exposure-response trend.
Liu et al. (2009); Taiwan	Case-control (case: 680)	Mortality (death registration system)	Monitoring stations (SO_2: NO_2; PM_{10}; O_3; CO)	Marital status, urbanization	A significant positive association between the levels of air pollution and bladder cancer mortality.

BMI: body mass index; LUR: land use regression; PM: particulate matter; OR: odds ratio; NO_2: nitrogen dioxide; O_3: ozone; CO: carbon monoxide; SO_2: Sulphur dioxide; H_2S: hydrogen sulfide; PM_{10}: particulate matters with diameter less than 10 micrometers; SEP: socio-economic position

‡: for each outcome, studies are ordered chronologically from most recent to older

888
889 **Table 2. Summary of finding for the association between exposure to air pollution and kidney and urinary system cancer risk**
890

First author (year); study location‡	Design; number of case/outcome	Case definition	Exposure assessment and metrics	Adjustment	Findings
Cong (2018); China	Ecologic study	Kidney cancer incidence (cancer registry)	Annual waste gas emissions (total volume of waste gas, industrial waste gas, other waste gas, SO_2, and soot)	Sex, number of doctors per 10,000 population, education, Engel's coefficient	A significant association for kidney cancer incidence. The effect size was higher for males.
Raaschou-Nielsen (2017); Europe	Cohort (outcome: 697)	Kidney cancer incidence (cancer registry)	LUR (PM_{10}; $PM_{2.5}$; $PM_{2.5}$ absorbance; NO_2; NO_x; traffic intensity; PM elements; organic carbon in PM)	Age, sex, calendar time; smoking, occupation, employment, and education; area-level socio-economic status	Higher HR in association with higher $PM_{2.5}$ concentration and $PM_{2.5}$ absorbance. HR of NO_x and traffic density on the nearest street were slightly above one. Effect estimates in non-movers were slightly stronger than movers.
Raaschou-Nielsen (2011); Denmark	Cohort (outcome: 95)	Kidney cancer incidence (cancer registry)	LUR (NO_x), presence of a major road within 50 m, Per 10^4 vehicle km/day within 200 m	BMI, smoking, hypertension, education, occupation	A significant increase in kidney cancer risk in crude models, but disappeared in the adjusted model.
Turner (2017); USA	Cohort (outcome: 927)	Kidney cancer mortality (Cause of death from the questionnaire)	LUR ($PM_{2.5}$; NO_2; O_3)	Age, gender, race, education, marital status; BMI; smoking, dietary intake, consumption of alcoholic beverages; occupational exposures	Significant positive associations of $PM_{2.5}$ in minimally and fully adjusted models. $PM_{2.5}$ results were only significant for men, never smokers, and those with at least high school education.
Ancona et al. (2015); Italy	Cohort (outcome: 54)	Kidney cancer mortality (registry of causes of death)	Dispersion modeling (PM_{10}; H_2S; SO_X)	Sex, age, education, occupation, civil status, area-based SEP index, and outdoor NO_2	No significant associations were found.

First author (year); study location‡	Design; number of case/outcome	Case definition	Exposure assessment and metrics	Adjustment	Findings
Cohen et al. (2018); Israel	Cohort (outcome: 74)	Urinary tract cancer incidence (linked to the National Cancer Registry)	LUR (NO_X)	Sex, smoking, neighborhood socioeconomic status, ethnicity, hypertension, diabetes, chronic heart and renal failure, hemoglobin levels	Non-significant and small positive association was found.
Wong et al. (2016); Hong-Kong	Cohort (outcome: 155)	Urinary cancer mortality (data linkage with death registration system)	LUR ($PM_{2.5}$)	Age, sex, BMI, smoking, exercise, education, personal monthly expenditure, percentage of older subjects, the percentage with tertiary education, monthly domestic household income, percentage of smokers, the ground radon level	No significant association was found neither in all subjects nor in stratified groups by sex and smoking status.

BMI: body mass index; LUR: land use regression; HR: hazard ratio; PM: particulate matter; OR: odds ratio; NO_2: nitrogen dioxide; O_3: ozone; CO: carbon monoxide; SO_2: Sulphur dioxide; H_2S: hydrogen sulfide; PM_{10}: particulate matters with diameter less than 10 micrometers; SEP: socio-economic position

‡: for each outcome, studies are ordered chronologically from most recent to older

898 **Table 3. Newcastle-Ottawa Scale (NOS) score for the cohort studies on the association between air pollution exposure and bladder,**
899 **kidney, and urinary cancer risk**

Outcome	Study (first author and year)	Representativeness	Selection of non-cohort	Exposure ascertainment	No outcome at the start	Comparability	Outcome assessment	Follow-up time	Follow-up adequacy	NOS score
Bladder cancer	Cohen et al. (2018)	0	1	1	1	1	1	1	1	7
	Turner et al. (2017)	1	1	1	1	2	1	1	0	8
	Collarile et al. (2017)	1	0	1	0	0	1	0	0	3
	Raaschou Nielsen et al. (2011)	1	1	1	1	1	1	1	1	8
	Pedersen et al. (2016)	1	1	1	1	2	1	1	1	9
	Ancona et al. (2015)	1	1	1	0	1	1	1	0	6
	Visser et al. (2004)	1	1	1	1	0	1	0	0	5
Kidney cancer	Turner et al. (2017)	1	1	1	1	2	1	1	0	8
	Raaschou Nielsen et al. (2011)	1	1	1	1	1	1	1	1	8
	Ancona et al. (2015)	1	1	1	0	1	1	1	0	6
	Pedersen et al. (2016)	1	1	1	1	2	1	1	1	9
Urinary tract cancer	Cohen et al. (2018)	0	1	1	1	1	1	1	1	7
	Wong et al. (2016)	1	1	1	1	2	1	1	1	9

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902 **Table 4. Newcastle-Ottawa Scale (NOS) score for the case-control studies on the association between air pollution exposure and**
903 **bladder, kidney, and urinary cancer risk**
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Outcome	Study (first author and year)	Case definition	Representativeness	Control selection	Control definition	Comparability	Exposure assessment	Same exposure method	Response rate	NOS score
Bladder cancer	Castano-Vinyals et al. (2008)	1	0	0	1	2	0	1	0	5
	Liu et al. (2009)	0	1	0	1	0	1	1	0	4
	Ho et al. (2010)	0	1	1	1	0	0	1	0	4
	Turner et al. (2019)	1	0	0	1	2	1	1	0	6

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908 **Table 5. Reported associations between exposure to outdoor air pollution exposure and bladder cancer risk**
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Reference : first author (year)	Site	Outcome	Pollutant	Population	Exposure categories‡	Type of effect size	Point estimate (95% CI)
Al-ahmadi et al. (2013)	Bladder	Incidence	NO_2	All	Unclear	CIR	0.22 (Unclear)
Collarile et al. (2017)	Bladder	Incidence	NO_2	Male	≤ 16.9 vs 16.9–19.6 ; [10,80- 25,50]	IRR	1.07 (0.86: 1.33)
Collarile et al. (2017)	Bladder	Incidence	NO_2	Female	≤ 16.9 vs 16.9–19.6 ; [10,80- 25,50]	IRR	1.02 (0.68: 1.54)
Collarile et al. (2017)	Bladder	Incidence	NO_2	Male	≤ 16.9 vs >19.6 ; [10,80- 25,50]	IRR	1.04 (0.84: 1.30)
Collarile et al. (2017)	Bladder	Incidence	NO_2	Female	≤ 16.9 vs >19.6 ; [10,80- 25,50]	IRR	**1.53 (1.03: 2.29)**
Pedersen et al. (2016)	Bladder	Incidence	NO_2	All	Per 10 µg.m^{-3}; 25,68 (14,29); [5,20- 53,20]	HR	0.98 (0.89: 1.08)
Turner et al. (2019)	Bladder	Incidence	NO_2	All	Per 14.2 µg.m^{-3}; 28,60 (10,20); [1,10- 58,60]	OR	0.97 (0.84: 1.13)
Cohen et al. (2018)	Bladder	Incidence	NO_x	All	Per 10 ppb; 19.5; [2,3- 79,7]	HR	1.07 (0.83: 1.37)
Pedersen et al. (2016)	Bladder	Incidence	NO_x	All	Per 20 µg.m^{-3}; 47,56 (28,45); [8,7- 96,4]	HR	0.99 (0.91: 1.09)
Raaschou-Nielsen (2011)	Bladder	Incidence	NO_x	All	Per 100 µg.m^{-3}; 28.4; [14,8- 69,4]	IRR	1.32 (0.80: 2.19)
Collarile et al. (2017)	Bladder	Incidence	PM_{10}	Male	≤ 40.6 vs 40.6-51.9 ; [19.6- 107.1]	IRR	1.10 (0.89: 1.36)
Collarile et al. (2017)	Bladder	Incidence	PM_{10}	Female	≤ 40.6 vs 40.6-51.9 ; [19.6- 107.1]	IRR	1.16 (0.78: 1.71)
Collarile et al. (2017)	Bladder	Incidence	PM_{10}	Male	≤ 40.6 vs >51.9 ; [19.6- 107.1]	IRR	1.00 (0.80: 1.25)
Collarile et al. (2017)	Bladder	Incidence	PM_{10}	Female	≤ 40.6 vs >51.9 ; [19.6- 107.1]	IRR	1.21 (0.80: 1.84)
Eitan et al. (2010)	Bladder	Incidence	PM_{10}	Male	Unclear ; [27,8- 41.2]	RR	0.82 (0.37: 1.07)
Eitan et al. (2010)	Bladder	Incidence	PM_{10}	Female	Unclear ; [28,8- 41.3]	RR	1.70 (0.25: 5.11)
Pedersen et al. (2016)	Bladder	Incidence	PM_{10}	All	Per 10 µg.m-3; 23,79 (11,82); [13,5- 46,4]	HR	0.92 (0.58: 1.48)
Pedersen et al. (2016)	Bladder	Incidence	$PM_{2.5}$	All	Per 5 µg.m-3; 14,62 (7,48); [7,1- 30,1]	HR	0.86 (0.63: 1.18)
Turner et al. (2019)	Bladder	Incidence	$PM_{2.5}$	All	Per 5.9 µg/m3; 15.8 (3.89); [7- 25.6]	OR	1.06 (0.71: 1.60)
Wang et al. (2019)	Bladder	Incidence	$PM_{2.5}$	All	Unclear	Correlation coefficient	0.85 (Unclear)
Collarile et al. (2017)	Bladder	Incidence	SO_2	Female	≤ 34.6 vs 34.6–37.5; [27,5- 85]	IRR	1.19 (0.80: 1.78)
Collarile et al. (2017)	Bladder	Incidence	SO_2	Female	≤ 34.6 vs >37.5; [27,5- 85]	IRR	1.39 (0.93: 2.08)
Collarile et al. (2017)	Bladder	Incidence	SO_2	Male	≤ 34.6 vs 34.6–37.5; [27,5- 85]	IRR	1.16 (0.94: 1.44)
Collarile et al. (2017)	Bladder	Incidence	SO_2	Male	≤ 34.6 vs >37.5; [27,5- 85]	IRR	1.02 (0.82: 1.27)
Eitan et al. (2010)	Bladder	Incidence	SO_2	Male	Unclear ; [1,8- 14,7]	RR	1.02 (0.30: 2.25)

Eitan et al. (2010)	Bladder	Incidence	SO_2	Female	Unclear; [1,8- 14,7]	RR	1.15 (0.22: 5.27)
Radespiel□Tröger et al.(2018)	Bladder	Incidence	PM_{10}	Male	Per 10 µg.m-3 ; 19.2 [12.7- 26.6]	RR	**1.19 (1.01–1.41)**
Radespiel□Tröger et al.(2018)	Bladder	Incidence	PM_{10}	Female	Per 10 µg.m-3; 19.2 [12.7- 26.6]	RR	**1.26 (1.09–1.47)**
Liu et al. (2008)	Bladder	Mortality	NO2	All	≤ 20.99 vs 21.19–26.87 ppb; Unclear	Unadjusted OR	**1.41 (1.08: 1.84)**
Liu et al. (2008)	Bladder	Mortality	NO_2	All	≤ 20.99 vs 27.33–44.85 ppb; Unclear	Unadjusted OR	**1.73 (1.27-2.36)**
Turner et al. (2017)	Bladder	Mortality	NO_2	All	Per 6.5 ppb; 11,6 (5,1); [1- 37,6]	HR	1.03 (0.94: 1.12)
Liu et al. (2009)	Bladder	Mortality	O_3	All	≤ 22.41 vs *22.42–25.06* ppb	Unadjusted OR	0.88 (0.68: 1.16)
Liu et al. (2009)	Bladder	Mortality	O_3	All	≤ 22.41 vs *25.11–35.70 ppb*	Unadjusted OR	1.07 (0.82: 1.39)
Turner et al. (2017)	Bladder	Mortality	O_3	All	Per 6.9 ppb; 38,2 (4); [26,7- 59,3]	HR	1.03 (0.93: 1.14)
Smith et al. (2016)	Bladder	Mortality	O_3	All	Unclear	Regression coefficient	0.01 (0.01: 0.02)
Ancona et al. (2015)	Bladder	Mortality	PM_{10}	Male	Per 0.027 ng; 0,02 (0,02); [0,02- 0,04]	HR	1.05 (0.70: 1.57)
Ancona et al. (2015)	Bladder	Mortality	PM_{10}	Female	Per 0.027 ng; 0,02 (0,02); [0,02- 0,04]	HR	1.53 (0.70: 3.36)
Liu et al. (2009)	Bladder	Mortality	PM_{10}	All	≤ 52.80 vs *53.04–71.72* ; Unclear	Unadjusted OR	1.08 (0.83: 1.41)
Liu et al. (2009)	Bladder	Mortality	PM_{10}	All	≤ 52.80 vs *72.24–90.29*; Unclear	Unadjusted OR	**1.39 (1.06: 1.83)**
Smith et al. (2016)	Bladder	Mortality	$PM_{2.5}$	All	Unclear	Regression coefficient	-0.01 (-0.02: 0.00)
Turner et al. (2017)	Bladder	Mortality	$PM_{2.5}$	All	Per 4.4µg.m-3; 12,6 (2,8); [1,4- 27,9]	HR	**1.13 (1.03: 1.23)**
Wang et al. (2019)	Bladder	Mortality	$PM_{2.5}$	All	Unclear	Correlation coefficient	-0.42 (Unclear)
Yeh et al. (2017)	Bladder	Mortality	$PM_{2.5}$	All	Per 1µg.m-3; Unclear	Regression coefficient	0.04 (0.04: 0.04)
Liu et al. (2009)	Bladder	Mortality	SO_2	All	≤ 4.32 vs *4.39–6.09*; Unclear	Unadjusted OR	**1.42 (1.10: 1.85)**
Liu et al. (2009)	Bladder	Mortality	SO_2	All	≤ 4.32 vs *6.49–17.87*; Unclear	Unadjusted OR	**1.73 (1.32: 2.27)**

For exposure categories: specified risk increase per how much of pollutant

‡: mean (SD); numbers in bracket are a range [lower range- upper range]

Table 6. Reported associations between exposure to outdoor air pollution exposure and kidney and urinary cancer risk

Reference: first author (year)	Site	Outcome	Pollutant	Population	Exposure categories‡	Type of effect size	Point estimate (95% CI)
Raaschou-Nielsen (2011)	Kidney	Incidence	NO_x	All	Per 100 µg.m-3 ; Unclear	IRR	1.73 (0.89; 3.73)
Raaschou-Nielsen (2017)	Kidney	Incidence	NO_x	All	Per 20 µg.m-3; 19.5; [2,3- 79,7]	HR	1.03 (0.93: 1.14)
Raaschou-Nielsen (2017)	Kidney	Incidence	PM_{10}	All	Per 10 µg.m-3; 21,97 (11,55); [13,5- 46,5]	HR	1.29 (0.85: 1.96)
Raaschou-Nielsen (2017)	Kidney	Incidence	$PM_{2.5}$	All	Per 5 µg.m-3; 13,94 (7,8); [7,1- 30,1]	HR	1.57 (0.81: 3.01)
Raaschou-Nielsen (2017)	Kidney	Incidence	NO_2	All	Per 10 µg.m-3; 24,32 (14,33); [5,2- 53,2]	HR	1.04 (0.92: 1.19)
Turner et al. (2017)	Kidney	Mortality	O_3	All	Per 6.9 ppb; 38,2 (4); [26,7- 59,3]	HR	0.97 (0.86: 1.09)
Turner et al. (2017)	Kidney	Mortality	$PM_{2.5}$	All	Per 4.4 µg.m-3; 12,6 (2,8); [1,4- 27,9]	HR	**1.14 (1.03: 1.27)**
Cohen et al. (2018)	Urinary tract	Incidence	NO_x	All	Per 10 ppb; 19.5; [2,3- 79,7]	HR	1.07 (0.88: 1.3)
Wong et al. (2016)	Urinary tract	Mortality	$PM_{2.5}$	All	Per 10µg.m-3; 33,7 (3,2); [26,1- 92,6]	HR	0.98 (0.58: 1.64)

For exposure categories: specified risk increase per how much of pollutant

‡: mean (sd); numbers in bracket are a range [lower range- upper range]

Table S1. The sample search algorithm used for literature search on outdoor air pollution exposure (as an exposure) and selected urological cancer incidence and/or mortality (as an outcome) on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Last updated on June 15, 2019.

#	Search query	Numbers of items found
1	(((((((((Urological[Title/Abstract]) OR Urologic[Title/Abstract]) OR Urinary Tract[Title/Abstract]) OR Kidney[Title/Abstract]) OR Renal[Title/Abstract]) OR Ureteral[Title/Abstract]) OR URETER[Title/Abstract]) OR Urethral[Title/Abstract]) OR URETHRA[Title/Abstract]) OR Bladder[Title/Abstract]	1044802
2	(((tumor[Title/Abstract]) OR neoplasm[Title/Abstract]) OR cancer[Title/Abstract]) OR malignancy[Title/Abstract]	2338139
3	1 and 2	147101
4	(((((("Kidney Neoplasms"[Mesh]) OR "Pelvic Neoplasms"[Mesh]) OR "Ureteral Neoplasms"[Mesh]) OR "Urinary Bladder Neoplasms"[Mesh]) OR "Urologic Neoplasms"[Mesh]) OR "Urethral Neoplasms"[Mesh]	135254
5	((("cancer incidence"[Title/Abstract]) OR "incidence of cancer"[Title/Abstract]) OR "cancer mortality"[Title/Abstract])	32351
6	3 or 4 or 5	244602
7	((((((((((((((((pm2.5[Title/Abstract]) OR pm10[Title/Abstract]) OR o3[Title/Abstract]) OR ozone[Title/Abstract]) OR no2[Title/Abstract]) OR "nitrogen dioxide"[Title/Abstract]) OR "carbon monoxide"[Title/Abstract]) OR so2[Title/Abstract]) OR "Sulfur dioxide"[Title/Abstract]) OR "Sulphur dioxide"[Title/Abstract]) OR "air pollutants"[Title/Abstract]) OR "air pollution"[Title/Abstract]) OR "particulate matter"[Title/Abstract]) OR "Ambient air"[Title/Abstract]) OR "Air quality"[Title/Abstract])) OR (((((("Air Pollution"[Mesh]) OR "Particulate Matter"[Mesh]) OR "Air Pollutants" [Mesh]) OR "Vehicle Emissions"[Mesh]) OR "Traffic-Related Pollution"[Mesh]))	200074
8	6 and 7	1513

938 **Table S2. Inclusion and exclusion criteria based on PECOS (population, exposure, comparison, outcome and study type) for a**
939 **systematic review on the association between outdoor air pollution exposure and risk of selected urological cancers**
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Decision	Population	Exposure	Comparison	Outcome	Type of study
Inclusion	Human; Adult	Ambient air pollution including a) specific pollutants (e.g. PM_{10}; $PM_{2.5}$; SO_2; NO_2; O_3; CO; NO_x) b) proxies (traffic; proximity index; …)	Not applicable	Selected urological cancers incidence/mortality (including kidney; bladder; urinary tract)	Prospective and retrospective cohort; case-control; ecologic studies
Exclusion	Children; Animal; Occupational cohorts	Occupational /Industrial air pollution exposure; geothermal and volcanic air pollution exposure; radioactive pollutants; radon; asbestos; pesticides; indoor air pollution; smoking-related products	Not applicable	Urinary cancer hospital admission; other urological cancers	Time series; case-report; reviews; in-vitro studies

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Table S3: GRADE assessment for the association between exposure to PM_{10} and risk of bladder cancer incidence

Domains	Assessment	Downgrading/ upgrading
Start level	Two cohorts, and two ecologic studies	High
Risk of bias	One of the cohorts suffering from different methodological issues such as insufficient follow-up period. In two ecologic studies, the adjustment is unclear.	Downgrade
Inconsistency	The values of effect sizes across the studies were inconsistent. The point estimates were in the range of 0.82 to 1.70, and confidence intervals were partially overlapped. However, in one of the estimates in the ecologic study, the upper confidence interval reached 5.11.	Downgrade
Indirectness	The exposure to air pollution allocated differently across different studies to the participants (LUR, dispersion modeling, and interpolation).	No change
Imprecision	Change in the direction of the decision at the two extremes of reported effect sizes.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias.	Unclear
Dose-response trend	One out of four studies analyzed a trend, however, found no linear trend.	No increase
Magnitude of associations	In all studies and reported associations, the magnitude of the effect sizes was below 1.4.	No increase
Residual confounding	Two ecologic studies suffering from the risk of exposure misclassifications.	No increase
Overall judgment	**Very low**	

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Table S4: GRADE assessment for the association between exposure to PM_{10} and risk of bladder cancer mortality

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort, one case-control study	High
Risk of bias	The case-control study suffering from non-clear case and control definition, exposure assessment, and adjustment. The cohort study also suffering from low follow-up duration and is not clear about the absence of outcome at the beginning of the study.	Downgrade
Inconsistency	The direction of the effect sizes are not opposite; however, the magnitudes are different.	No change
Indirectness	All of the studies conducted on the general population and the outcomes drawn from death registries.	No change
Imprecision	Change in the direction of the decision at the two extremes of reported effect sizes.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias.	Unclear
Dose-response trend	One of the studies reported a dose-response association.	Upgrade
Magnitude of associations	Two studies reported effect sizes with a magnitude below 1.4.	No increase
Residual confounding	One of the studies used readings from monitoring stations for exposure allocation. Also, one study just reported a crude association.	No increase
Overall judgment	**Low**	

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Table S5: GRADE assessment for the association between exposure to $PM_{2.5}$ and risk of bladder cancer incidence

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort, one case-control, and one ecologic study	High
Risk of bias	The cohort study summarized the results of several other cohorts and has a good NOS score. However, the case-control suffering from representativeness and appropriate selection of controls.	No change
Inconsistency	The direction and magnitude of the effect sizes across the studies were inconsistent. The point estimates were varying and confidence intervals were partially overlapped.	Downgrade
Indirectness	Exposure to air pollution, population, and outcome were in accordance with the review aim.	No change
Imprecision	The point estimates and confidence intervals were not consistent. The number of studies is not sufficient.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were not able to test it objectively.	Unclear
Dose-response trend	None of the studies reported the dose-response.	No increase
Magnitude of associations	In all studies and reported association, the magnitude of the effect sizes was below 1.4.	No increase
Residual confounding	No sign of exposure misclassification.	No increase
Overall judgment	**Very Low**	

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Table S6: GRADE assessment for the association between exposure to $PM_{2.5}$ and risk of bladder cancer mortality

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort, three ecologic studies	Low
Risk of bias	Most of the studies were ecologic and the source of outcome data was not clear in one of them. Due to the nature of ecologic studies, the risk of bias was high.	Downgrade
Inconsistency	Direction and the value of the effect sizes were different across studies.	Downgrade
Indirectness	The methods of exposure assessment and allocation across the studies were different. However, the population and outcome were similar.	No change
Imprecision	The point estimates and confidence intervals were not consistent.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were not able to check it objectively.	Unclear
Dose-response trend	None of the studies reported the dose-response trend.	No change
Magnitude of associations	The magnitude of effect sizes was large enough to upgrade the level of evidence.	No change
Residual confounding	Three studies used area-level measures of exposure.	No change
Overall judgment	**Very low**	

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Table S7: GRADE assessment for the association between exposure to NO_2 and risk of bladder cancer incidence

Domains	Assessment	Downgrading/ upgrading
Start level	Two cohorts, one case-control, and one ecologic study	High
Risk of bias	Three out of four studies suffering from different methodological issues including representativeness of the population, control selection, or inadequate control of confounding. Therefore, most of the information is coming from studies with a high risk of bias.	Downgrade
Inconsistency	The point estimates were different and confidence intervals were partially overlapped. The confidence intervals were reasonable except in the case of the ecologic study.	Downgrade
Indirectness	Exposure to air pollution allocated differently across the studies (LUR, dispersion modeling, and ecologic approaches). However, in general, the population, exposure, and exposure were in accordance with the PECO.	No change
Imprecision	Decision based on each side of the confidence intervals was associated to a different judgment.	Downgrade
Publication bias	Given the comprehensive search and size of the sample in the published studies we decided little even no publication bias.	Unclear
Dose-response trend	One out of four studies conducted the categorized analyses based on exposure intensity. However, the observed trend in the groups was not similar in males and females.	No change
Magnitude of associations	In all reported associations, the magnitude of the effect sizes was large enough to lead to an upgrade of evidence.	No change
Residual confounding	In two out of four studies the confounding adjustment was not clear. We think adjustment would decrease the observed strength of observed associations.	No change
Overall judgment	**Very low**	

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Table S8: GRADE assessment for the association between exposure to NO_2 and risk of bladder cancer mortality

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort, one case-control study	High
Risk of bias	The case-control study suffering from different methodological issues including case definition, control selection, unclear response rate, and inadequate control of confounders. The cohort study suffering from the inadequacy of follow-up.	Downgrade
Inconsistency	The direction of effect sizes are similar for both studies, but the point estimates are different.	No change
Indirectness	Both studies conducted on the general population and the outcomes drawn from death registries. The exposure assessment in the case-control study was not as precise as the cohort (it was based on station reading in the case-control study).	No change
Imprecision	The effect estimates in the case-control were precise. However, in the cohort study, there was impreciseness in the reported effect sizes.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were not able to systematically assess the publication bias by statistical tests or visual plots.	Unclear
Dose-response trend	One of the studies reported dose-response data.	Upgrade
Magnitude of associations	In one case-control study, the magnitude of the effects was above 1.4.	No increase
Residual confounding	Considering possible exposure misclassification in using monitoring stations readings for exposure allocation, effect estimates would shift to null.	No increase
Overall judgment	**Low**	

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Table S9: GRADE assessment for the association between exposure to NO_x and risk of bladder cancer incidence

Domains	Assessment	Downgrading/ upgrading
Start level	Three cohort studies	High
Risk of bias	The overall risk of bias in all three cohorts was low. Adjustment for sex and age in one of the cohorts and also representativeness of the population in another cohort were problematic.	Downgrade
Inconsistency	The magnitude of the point estimate risks in the studies was different (ranged from 0.99 to 1.32). Two of cohorts reported an increase (even though at different magnitude) and one other reported a trivial decrease (0.99)	Downgrade
Indirectness	The population of interest in one of the studies were from cardiac patients and did not completely cover the population of interest in this study.	Downgrade
Imprecision	All three cohorts have reported this exposure-outcome association, but decide on both sides of the confidence intervals will lead to a different judgment.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were not able to systematically assess the publication bias by statistical tests or visual plots.	Unclear
Dose-response trend	No report.	No change
Magnitude of associations	The magnitude of the observed effects was not large enough to leads to an upgrade.	No change
Residual confounding	The risk of exposure misclassification is low in all three studies.	Upgrade
Overall judgment	**Very Low**	

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Table S10: GRADE assessment for the association between exposure to SO_2 and risk of bladder cancer incidence

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort and one ecologic study	High
Risk of bias	The risk of bias in the cohort study was high. Also considering the low quality of ecologic studies *per se*, the overall quality of methodological issues is not satisfactory.	Downgrade
Inconsistency	The point estimate of the observed risk in studies was 1.02 to 1.39 however all of them reported an increase in the risk. The confidence intervals (especially in the ecologic study) are wide.	Downgrade
Indirectness	Given the ecologic allocation of exposure to the population in one of the studies, there is a heterogeneity in the exposure assessment methods.	Downgrade
Imprecision	The number of studies is limited (n=2). The judgment will be changed according to the selection of each side of the confidence interval.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were unable to objectively evaluate the possible publication bias.	Unclear
Dose-response trend	No report.	No change
Magnitude of associations	In all reported associations the magnitude of the effect sizes was below 1.4.	No change
Residual confounding	Not enough for upgrading.	No change
Overall judgment	**Very low**	

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Table S11: GRADE assessment for the association between exposure to O_3 and risk of bladder cancer mortality

Domains	Assessment	Downgrading/ upgrading
Start level	One cohort and one case-control and one ecologic	High
Risk of bias	The risk of bias in the case-control study was high due to no exact definition of cases and controls. Follow-up time in the cohort was not sufficient.	Downgrade
Inconsistency	The magnitude of observed risk in the studies was 0.88 to 1.07. The observed effect sizes in the case-control study were opposite at different doses of exposure.	Downgrade
Indirectness	The population and outcome were in accordance with the PECO. However, the exposure assessment methods in the studies were different.	No change
Imprecision	The judgment will be changed according to the selection of each side of the confidence intervals.	Downgrade
Publication bias	Given the comprehensive search, it seems little even no publication bias. However, we were unable to objectively evaluate the possible publication bias.	Unclear
Dose-response trend	No report.	No change
Magnitude of associations	The magnitude of the observed effect sizes was not large enough to upgrade the evidence.	No change
Residual confounding	A case-control study has used exposure data from monitoring stations, which can introduce misclassification bias.	No change
Overall judgment	**Very low**	

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Highlights:

- Few studies – ecological, case-control and cohorts - were eligible.
- Limitation issues of the studies prevented the meta-analysis realization.
- Positive association between air pollution and bladder and kidney cancer risk were showed.
- For bladder cancer, mortality evidences were stronger than the incidence.
- Future studies should be rigorous with adjustment, exposure assessment methods and follow-ups.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: