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Outdoor air pollution and risk for kidney parenchyma cancer in 14 European cohorts

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Running title: Air pollution and kidney parenchyma cancer

What's new?

Ambient air pollution is an established cause of lung cancer. It is of considerable public health interest whether air pollution also causes other cancers. A few studies indicated that air pollution might cause kidney cancer. These authors investigated a possible link between kidney parenchyma cancer and air pollution at the residence of 289,002 participants of 14 European cohorts. They found an increased risk in association with particulate matter air pollution, although not statistically significant.

Conflicts of interest

Bente Oftedal declares to own shares in three Norwegian companies: Statoil (oil and gas), Telenor (telecom) and Hafslund ASA (energy). However, she is not aware that this ownership has affected her scientific work or judgement.

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Abstract

Several studies have indicated weakly increased risk for kidney cancer among occupational groups exposed to gasoline vapors, engine exhaust, polycyclic aromatic hydrocarbons and other air pollutants, although not consistently. It was the aim to investigate possible associations between outdoor air pollution at the residence and the incidence of kidney parenchyma cancer in the general population. We used data from 14 European cohorts from the ESCAPE study. We geocoded and assessed air pollution concentrations at baseline addresses by land-use regression models for particulate matter (PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5}$ absorbance (soot)) and nitrogen oxides (NO_2, NO_x), and collected data on traffic. We used Cox regression models with adjustment for potential confounders for cohort-specific analyses and random effects models for meta-analyses to calculate summary hazard ratios (HRs). The 289,002 cohort members contributed 4,111,908 person-years at risk. During follow-up (mean 14.2 years) 697 incident cancers of the kidney parenchyma were diagnosed. The meta-analyses showed higher HRs in association with higher PM concentration, e.g. HR=1.57 (95%CI: 0.81-3.01) per 5μg/m^3 $PM_{2.5}$ and HR=1.36 (95%CI: 0.84-2.19) per $10^{-5}m^{-1}$ $PM_{2.5}$ absorbance, albeit never statistically significant. The HRs in association with nitrogen oxides and traffic density on the nearest street were slightly above one. Sensitivity analyses among participants who did not change residence during follow-up showed stronger associations, but none were statistically significant. This study provides suggestive evidence that exposure to outdoor PM at the residence may be associated with higher risk for kidney parenchyma cancer; the results should be interpreted cautiously as associations may be due to chance.

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INTRODUCTION

A working group established under the International Agency for Research on Cancer recently classified outdoor air pollution in general, and particulate matter (PM) in particular, as carcinogenic to humans [1]. This classification was based on, among others, an extensive review of the epidemiological literature, which provided convincing evidence for an association with lung cancer. Positive associations were also noted for cancer of the urinary bladder and childhood leukaemia, whereas associations between air pollution and other cancers had only been sparsely studied [1].

Over 90% of kidney cancers develop in the kidney parenchyma and the vast majority of these are adenocarcinomas (often denoted as renal cell carcinomas); the less than 10% of kidney cancers, which develops in the renal pelvis, are primarily of the transitional cell type [2]. Worldwide, the incidence rates of kidney cancer increased until the mid-1990s when they plateaued or declined in many countries [2]. Incidence rates of kidney parenchyma cancer are relatively high in Europe with rates between 3 and 15 per 100,000 in different countries [2]. Active tobacco smoking, obesity and hypertension are established risk factors for cancer of the kidney parenchyma [2,3] and there is also suggestive evidence for, among others, exposure to environmental tobacco smoke [4,5]. Several studies of occupational groups, such as transport workers, drivers, policemen, metal foundry workers, and gasoline service station workers exposed to gasoline vapors, engine exhaust, polycyclic aromatic hydrocarbons, and other air pollutants, have indicated weakly increased risk for kidney cancer [6-8], although the literature is neither consistent [9] nor conclusive [10]. Garcia-Perez et al. found higher kidney cancer mortality in Spanish general populations exposed to ambient air pollution from incinerators and hazardous waste treatment plants [11] and a cohort study of a general Danish population found positive but statistically insignificant

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associations between nitrogen oxides (NO_x) at the residence and kidney cancer incidence but no association with amount of street traffic near the residence [12]. Further, ultrafine particles can translocate from the airways to the kidney and other organs of experimental animals [13] and experiments have shown that diesel particles can induce cancer-relevant processes in the kidneys [14,15].

We recently reported from the European Study of Cohorts for Air Pollution Effects (ESCAPE) that PM in outdoor air with a diameter < 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$) at the residence is associated with risk for the development of lung cancer [16] and natural-cause mortality [17].

The aim of the present study was to investigate a possible association between outdoor air pollution and the risk for cancer of the kidney parenchyma in general European populations, applying the methods developed in ESCAPE.

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MATERIALS AND METHODS

Design and participants

The full ESCAPE study included 12 European areas where air pollution measurements were performed, land use regression (LUR) models were developed, and adult cohort studies with cancer incidence data were located. The present study included the 14 cohorts, located in 10 areas, with information on incident cancer, the most important potential confounders, with at least 20 incident kidney parenchyma cancer cases during follow-up and where the resources needed for participation were available. The 14 cohorts were in Sweden (European Prospective Investigation into Cancer and Nutrition[EPIC]-Umeå, Swedish National Study on Aging and Care in Kungsholmen [SNAC-K], Stockholm Screening Across the Lifespan Twin Study and TwinGene [SALT], Stockholm 60 years old and IMPROVE study [60-y/IMPROVE], Stockholm Diabetes Prevention Program [SDPP]), Norway (Oslo Health Study [HUBRO]), Denmark (Diet, Cancer and Health Study [DCH]), the Netherlands (EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [MORGEN], EPIC-PROSPECT), the United Kingdom (EPIC-Oxford), Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]), Italy (EPIC-Varese, EPIC-Turin) and Spain (EPIC-San Sebastian); Figure 1). Our previous study on lung cancer included 312,944 participants of 17 cohorts in 12 study areas. The present study on kidney parenchyma cancer included 289,002 participants, i.e. a large fraction of our previous study. Most of the study areas were large cities and the surrounding suburban or rural communities, as specified in the online appendix (pp. 4–13). A pooled analysis of all cohort data was not possible due to data-transfer and privacy issues but data from the four Stockholm cohorts (SNAC-K, SALT, 60-y/IMPROVE and SDPP) were pooled, and analysed and denoted as one cohort (Cardiovascular Effects of Air pollution and Noise in Stockholm [CEANS]) in the following.

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Similarly, data from the two cohorts from the Netherlands (EPIC-MORGEN and EPIC-PROSPECT) were pooled, analysed and denoted as one [EPIC-NL]. Thus, ten cohort data sets were analysed. Information on lifestyle etc. among cohort participants was obtained by questionnaires or interviews at enrolment (see online appendix, Table S1). The local ethical and data protection authorities approved the use of cohort data. All participants signed informed consent forms at enrolment.

Definition of incident cancer of the kidney parenchyma

We included cancers located in the kidney parenchyma (ICD10/ICDO3: C64). We only included primary cancers (i.e. not metastases). The cohort members were followed up for cancer incidence in national or local cancer registries.

Exposure assessment

Annual outdoor air pollution concentrations at the baseline residential addresses of study participants were estimated by LUR models in a three-step, standardized procedure that has been described elsewhere [18,19]. First, PM with an aerodynamic diameter < 10 μm (PM_{10}), PM with aerodynamic diameter < 2.5 μm ($PM_{2.5}$), $PM_{2.5}$ absorbance (a marker for black carbon and soot), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) were measured three times during different seasons at locations for each cohort population for 1 year between October 2008 and April 2011. Coarse PM was calculated as the difference between PM_{10} and $PM_{2.5}$. In the Umeå, Varese and San Sebastian areas only NO_2 and NO_x was measured. Results from the three measurements were averaged, adjusting for temporal trends using data from a background monitoring site with continuous data [18,20]. PM filters were weighed before and after each measurement centrally at IRAS, Utrecht University. Second, we collected information about potential predictor variables relating to nearby traffic intensity, population/household

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density and land use from Geographic Information Systems (GIS), and evaluated these to explain spatial variation of annual average concentrations using regression modelling [18,19]. In general, predictors for PM_{10}, $PM_{2.5}$, NO_x and NO_2 related to traffic/roads and population/building density. Variables related to industry, port and altitude were also predictors in some models. These LUR models were evaluated using Leave-One-Out-Cross-Validation, which successively leaves one site out of the data and refits the model with the remaining N-1 sites. The models generally explained a large fraction of measured spatial variation, the r^2 from leave-one-out cross-validation usually falling between 0.60 and 0.80 [16]. Finally, we used the models to assess exposure at the baseline address of each cohort member. If values of predictor variables for the cohort addresses were outside the range of values for the monitoring sites, we truncated the values to the minimum or maximum values at the monitoring sites. We truncated to prevent unrealistic predictions (e.g. related to too small distance to roads in GIS) and because we did not want to extrapolate the derived model beyond the range, for which it was developed. Truncation has been shown to improve predictions at independent sites [21]. We also collected information on traffic intensity (vehicles/day) on the nearest street. As part of the TRANSPHORM project, we used similar methods to predict concentrations of eight elements in PM at participants' baseline addresses [22,23]; we describe these procedures in the online appendix (pp. 2).

Statistical analyses

The association between long-term exposure to air pollution and incidence of kidney parenchyma cancer was analysed in each cohort separately at the local centre by common standardized protocols for exposure assessment, outcome definition, confounder models and statistical analyses. Cohort-specific effect estimates were combined by meta-analysis at the Danish Cancer Society Research Center, Copenhagen, Denmark.

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We fitted Cox proportional hazards regression models for each cohort, with age as the underlying time scale and followed up participants from enrolment until the time of a kidney parenchyma cancer diagnosis or censoring. We excluded participants with a cancer (except non-melanoma skin cancer) before enrolment and censored at the time of death, a diagnosis of any other cancer (except non-melanoma skin cancer), emigration, or end of follow-up, whichever came first. We censored participants with another cancer because cancer treatment and change of life style might change the subsequent risk for development of another cancer. Air pollution exposure was analysed as a linear variable in three a-priori specified confounder models. Model 1 included sex, calendar time (year of enrolment; linear) and age (time axis). Model 2 additionally adjusted for smoking status (never/former/current), smoking intensity (g tobacco/day), smoking duration (years), occupation/employment status (different definitions, see online appendix pp. 3-13), educational level (low, medium, high), body mass index (BMI) (linear, kg/m^2) and hypertension (yes/no) (all referring to baseline). Model 3 (the main model) further adjusted for area-level socio-economic status. Information on at least age, sex, calendar time, smoking status, smoking intensity, smoking duration and BMI was available in all cohorts. We provide further information on the available variables and their definition and distribution in each cohort in the online appendix (pp. 4-13 and Table S1). Potential confounders were based on previous literature on risk factors for kidney cancer and availability.

We undertook a number of sensitivity analyses for each cohort, all with confounder model 3. First, we repeated the analyses after restriction to participants who had lived at the baseline address throughout the follow-up period, thus reducing misclassification of long-term exposure to air pollution in this sub-population. Secondly, we added an indicator of degree of urbanization. Thirdly, we tested the linear

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assumption in the relation between each air pollutant and kidney parenchyma cancer by replacing the linear term with a natural cubic spline with three equally spaced inner knots, and compared the model fit of the linear and the spline models by the likelihood-ratio test. Fourthly, we repeated the analyses using back-extrapolated NO_2 and NO_x exposure data, which is described further in the online appendix (pp. 2-3).

In the meta-analysis, we used random-effects models to summarize the results for cohorts [24]. I^2 statistics [25] and *p* values for the χ^2 test from Cochran's Q were calculated to determine heterogeneity among cohort-specific effect estimates. We used a common STATA (www.stata.com) script for all analyses.

RESULTS

Fourteen cohorts in seven European countries contributed to this study. Altogether 289,002 cohort members contributed 4,111,908 person-years at risk and 697 incident kidney parenchyma cases were registered during follow-up (mean, 14.2 years). The number of participants and cases varied considerably, the Austrian cohorts contributing almost half the cases (Table 1). The cohort areas represented a wide range of exposures, with 3–11 times higher mean air pollution concentrations in some Southern than Northern areas (Table 1). The variation in exposure within study areas was substantial, as shown previously [16]. The mean age at enrolment varied from 43 to 57 years (Table 1).

The meta-analyses showed higher summary hazard ratios (HRs) in association with higher PM

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concentration, e.g. HR=1.57 (95% CI: 0.81-3.01) per 5μg/m^3 $PM_{2.5}$ and HR=1.36 (95% CI: 0.84-2.19) per $10^{-5}m^{-1}$ $PM_{2.5}$ absorbance (soot), albeit never statistically significant (Table 2). The HRs in association with nitrogen oxides and traffic were slightly above one. Adjustment did not affect the summary HRs much (Table 2). The summary HRs for PM_{10}, PM coarse and $PM_{2.5}$ were based on low to moderate heterogeneity between cohort-specific results; all p values for heterogeneity were ≥0.10 (Table 2). For the large VHM&PP cohort, HRs in association with $PM_{2.5}$ and $PM_{2.5}$ absorbance were lower than one ($PM_{2.5}$ HR=0.73; 95% CI: 0.47-1.14); all other cohorts showed increased risk in association with $PM_{2.5}$ exposure (Figure 2 and online Figure S1). Analyses based on participants who did not change residence during follow-up showed stronger associations, but none was statistically significant (Table 3). These results were based on stronger heterogeneity, which were statistically significant for $PM_{2.5}$ and PM_{10} ($p \leq 0.01$) (Table 3).

The assumption of linearity was not violated (online Table S2). Adjustment for degree of urbanization did not affect the results much (online Table S3) and use of back-extrapolated NO_2 and NO_x data only affected the results marginally (online appendix pp. 2-3 and Table S4).

Explorative analyses of 8 PM elements in two particle fractions (PM_{10} and $PM_{2.5}$) showed mostly elevated HRs. HRs were elevated in both particle fractions for Cu, Fe, Zn, V and Si. With the exception of an HR of 2.17 (95% CI: 1.19-3.97) per 100 ng/m^3 vanadium in PM_{10}, none of the HRs were statistically significant (online Table S5). Restriction to cohort participants who lived at the same residence during follow-up provided mostly higher HRs for the PM elements (online Table S5).

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DISCUSSION

This study showed elevated summary HRs for kidney parenchyma cancer incidence in association with higher concentration of four different measures of PM air pollution, albeit never statistically significant. The HRs in association with nitrogen oxides and traffic were close to one. Sensitivity analyses among participants who did not change residence during follow-up showed stronger associations, but none was statistically significant.

Our study benefited from a large number of cohort participants from general populations with widely different levels of air pollution and complete follow-up. The strengths of our study also include the use of standardized methods for exposure assessment and data analyses across all cohorts. We adjusted the analyses for a number of potential confounders. In particular, all cohort-specific analyses were adjusted for the important smoking variables smoking status, smoking intensity and smoking duration, but the possibility of residual confounding cannot be excluded. We assessed a comprehensive set of pollutants at address-level and the individual exposure assessment was based on actual measurements made in the development of LUR models for the detection of within-area contrasts. Since pooling of data across all cohorts was not possible we could not take full advantage of the exposure contrasts across Europe.

In the present study, the HRs for kidney parenchyma cancer were actually larger than those reported in the ESCAPE study for lung cancer, which were 1.22 (1.03,1.45), 1.18 (0.96,1.46) and 1.12 (0.88,1.42) for PM_{10}, $PM_{2.5}$ and $PM_{2.5}$ absorbance [16]. The confidence intervals of the HRs for kidney parenchyma cancer were wider, however, which is likely due to the smaller number of cases (697 kidney parenchyma versus 2095 lung cancer cases); the person time under risk was virtually the same. A previous study found an increased HR for kidney cancer in association with NO_x at the residence [12],

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which was not found in the present study. Our finding of non-significantly elevated HRs could be affected by a combination of the number of cancer cases, misclassification of exposure, confounding and chance. Several factors may have contributed to misclassification of the exposure. Although our LUR models performed well, with leave-one-out-cross-validation r^2 values typically between 0.6 and 0.8 [16], any model incorporates some degree of misclassification. Also, we used data on air pollution for 2008–2011 in developing our LUR models but applied them to baseline addresses mainly 10–15 years earlier. Recent research in Rome, the Netherlands and Vancouver has shown that the spatial distribution of air pollution is relatively stable over 10–year periods [26-28], a study showed high correlations between traffic intensities on Dutch streets over a 10 year period [29] and spatial models for black smoke in the United Kingdom provided reasonable predictions even going back to the 1960s [30], indicating that more recent estimations reflect also historical exposure contrasts. In our study, exposure was assessed at the enrolment address; moving from that address during follow-up might lead to misclassification of the exposure relevant to later development of cancer. Our results show stronger associations between air pollution and the risk for kidney parenchyma cancer among people who lived at the same address throughout follow-up, which would be expected if air pollution truly causes kidney parenchyma cancer. Altogether, we would expect the exposure misclassification in our study to be non-differential and consequently not to create artificial associations but rather to influence the HRs towards unity. The previously reported associations between air pollution and all-cause mortality [17] and lung cancer [16] using the same exposure assessment method as in the present study indicates that the method indeed detects effects of exposure contrasts.

The airways are the primary target organs for inhaled particles but evidence from experimental studies with animals shows that ultrafine particles can translocate to other organs, such as the liver, kidneys,

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heart and brain [13,31-33]. Although the amount of particles accumulating in secondary target organs, such as the kidney, is many times lower than the lung tissue dose, it may be relevant for carcinogenic processes [34,35]. Experimental evidence supports that diesel particles induce cancer-relevant processes in the kidneys: diesel exhaust particles induced oxidative stress in cultured human kidney cells [14] and exacerbated renal oxidative stress, inflammation and DNA damage in mice [15]. We are aware of no previous studies on outdoor PM air pollution and kidney cancer in general populations.

The explorative analyses of 8 PM elements showed mostly non-significantly elevated HRs for copper, iron, zinc, vanadium and silicon for both particle fractions. The vanadium content of $PM_{2.5}$ was significantly associated with risk for kidney parenchyma cancer, with substantially elevated HRs in both PM_{10} and $PM_{2.5}$. This may point to a specific source of particles. However, we do not want to over-interpret the vanadium findings as one significant association is close to what would be expected by chance among the 16 tests undertaken for the PM element analyses, given our 5% significance level. Each PM element can be considered as representing different air pollution sources with copper, iron and zinc being indicators mainly of non-tailpipe traffic emissions such as brake and tyre wear, sulphur mainly indicating long-range transport, nickel and vanadium indicating mixed oil-burning and industry, silicon crustal material and potassium biomass burning [22,36-38].

The Austrian VHM&PP cohort was the only cohort where $PM_{2.5}$ and $PM_{2.5}$ absorbance (soot) was not associated with higher risk for kidney parenchyma cancer (Figure 2 and online Supplementary Figure S1). This large cohort influenced the summary HRs substantially: without the VHM&PP cohort, the summary HR was 1.95 (1.21, 3.14) for $PM_{2.5}$. We cannot explain the opposite results with any bias or design issue related to specifically this cohort; chance might be the explanation. The latter

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interpretation is supported by the fact that in the lung cancer and all-cause mortality ESCAPE analyses, elevated HRs were found for this cohort, that did not affect the summary HRs [16,17]. A post-hoc explanation could be that the concentrations of vanadium were lowest in this cohort, while vanadium was associated with the highest HRs among the analyzed PM elements.

In conclusion, this study provides suggestive evidence that exposure to outdoor PM at the residence may be associated with higher risk for kidney parenchyma cancer. The result should be interpreted with caution and future studies are needed to confirm or reject this hypothesis.

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SUPPLEMENTARY DATA

Supplementary data are available online.

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FIGURE LEGENDS

Figure 1. Areas where cohort members lived, measurements were taken and land-use regression models for prediction of air pollution were developed.

Figure 2. Cohort-specific associations between $PM_{2.5}$ (upper Forest plot, HRs per 5 $\mu g/m^3$), NO_2 (lower Forest plot, HRs per 10 $\mu g/m^3$) and risk for kidney parenchyma cancer

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Table 1. Participants, kidney cancer cases, mean air pollution concentrations, and traffic in cohorts.

Cohort, location	$N_{participants}$	Mean age at baseline (years)	Person-years at risk	N_{cases}	PM_{10} ($\mu g/m^3$)	PM_{coarse} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	$PM_{2.5}abs$ (10^{-5} m^{-1})	NO_2 ($\mu g/m^3$)	NO_x ($\mu g/m^3$)	Traffic on nearest street (vehicles/day)
EPIC-Umeå, Umeå, Sweden	21 596	46	290 220	30	NA	NA	NA	NA	5.2	8.7	845
HUBRO, Oslo, Norway	17 786	48	151 559	21	13.5	4.0	8.9	1.2	20.9	38.2	2495
CEANS, Stockholm, Sweden	17 161	56	179 913	43	14.6	7.1	7.1	0.6	10.7	18.9	1531
DCH, Copenhagen, Denmark	37 643	57	556 466	125	17.2	5.7	11.3	1.2	16.4	26.8	3023
EPIC-NL, the Netherlands	30 120	50	355 756	46	25.4	8.5	16.8	1.4	25.2	37.9	1292
EPIC-Oxford, London/Oxford, United Kingdom	35 886	45	392 233	22	16.0	6.4	9.8	1.1	24.4	40.8	1392
VHM&PP, Voralberg, Austria	103 347	43	1 873 157	324	20.6	6.7	13.6	1.7	19.9	39.9	1685
EPIC-Varese,	10 299	52	111 092	29	NA	NA	NA	NA	43.5	86.7	NA

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Varese, Italy											
EPIC-Turin, Turin, Italy	7578	54	108 716	22	46.5	16.5	30.1	3.1	53.2	96.4	4018
EPIC-San Sebastian, San Sebastian, Spain	7586	49	92 796	35	NA	NA	NA	NA	23.8	47.2	NA

$PM_{2.5}$abs, $PM_{2.5}$absorption

NA, not available

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Table 2. Random-effects meta-analyses hazard ratios for kidney parenchyma cancer in association with exposure to six air pollutants and a traffic indicator and measures of heterogeneity between underlying cohort-specific results.

Exposure	Increase	No. of Cohorts[1]	HR (95% CI)			Measures of heterogeneity between cohorts	
			Model 1[2]	Model 2[3]	Model 3[4]	Model 3	
						I^2 (%)	p[5]
PM_{10}	10 μg/m^3	7	1.40 (0.87-1.51)	1.39 (0.87-2.20)	1.29 (0.85-1.96)	25	0.24
$PM_{2.5}$	5 μg/m^3	7	1.46 (0.81-2.61)	1.48 (0.81-2.70)	1.57 (0.81-3.01)	44	0.10
PM_{coarse}	5 μg/m^3	7	1.11 (0.82-1.51)	1.12 (0.80-1.56)	1.08 (0.80-1.45)	0	0.53
$PM_{2.5}$ absorbance	10^{-5} m^{-1}	7	1.43 (0.89-2.31)	1.54 (0.90-2.63)	1.36 (0.84-2.19)	25	0.24
NO_2	10 μg/m^3	10	1.06 (0.93-1.21)	1.10 (0.94-1.28)	1.04 (0.92-1.19)	13	0.32
NO_x	20 μg/m^3	10	1.03 (0.93-1.14)	1.04 (0.94-1.15)	1.03 (0.93-1.14)	0	0.69
Traffic density on nearest street	5000 vehicles per day	8	1.03 (0.95-1.11)	1.02 (0.95-1.10)	1.02 (0.95-1.10)	0	0.87

Within each cohort, we included only participants without missing data in any of the variables included in model 3, thus using an identical data set for analyses with all three models within the same cohort.

[1] The four Stockholm cohorts were pooled and only count one. Similarly, the two Dutch EPIC cohorts were pooled and only count one.

[2] Model 1: age (time scale in Cox model), sex, calendar time

[3] Model 2: Model 1 + smoking status, smoking intensity, smoking duration, occupation/employment status, educational level, BMI, hypertension

[4] Model 3: Model 2 + area-level socio-economic status

[5] Cochran test for heterogeneity

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Table 3. Random-effects meta-analyses hazard ratios for kidney parenchyma cancer in association with exposure to six air pollutants and a traffic indicator for all participants and for those with the same residence during the whole follow-up period (non-movers). All results derive from analyses with confounder model 3[1].

Exposure	Increase	HR (95% CI)			Measures of heterogeneity between cohorts	
		All cohorts; all participants (repeated for comparison)	Cohorts with non-mover information[2]; all participants	Cohorts with non-mover information; non-movers	Cohorts with non-mover information; non-movers	
					I^2 (%)	p-value[3]
PM_{10}	10 μg/m^3	1.29 (0.85-1.96)	1.33 (0.82-2.17)	1.72 (0.73-4.08)	68	0.01
$PM_{2.5}$	5 μg/m^3	1.57 (0.81-3.01)	1.73 (0.72-4.18)	2.62 (0.68-10.1)	74	0.003
PM_{coarse}	5 μg/m^3	1.08 (0.80-1.45)	1.15 (0.82-1.59)	1.45 (0.92-2.30)	20	0.29
$PM_{2.5}$ absorbance	10^{-5} m^{-1}	1.36 (0.84-2.19)	1.37 (0.71-2.65)	1.67 (0.75-3.71)	38	0.16
NO_2	10 μg/m^3	1.04 (0.92-1.19)	0.99 (0.86-1.15)	1.08 (0.82-1.43)	51	0.07
NO_x	20 μg/m^3	1.03 (0.93-1.14)	1.00 (0.90-1.12)	1.04 (0.81-1.34)	51	0.07
Traffic density on nearest road	5000 vehicles per day	1.02 (0.95-1.10)	1.03 (0.95-1.11)	1.04 (0.94-1.16)	0	0.74

[1] Model 3: age (time scale in Cox model), sex, calendar time, smoking status, smoking intensity, smoking duration, occupation/employment status, educational level, BMI, hypertension, area-level socio-economic status

[2] EPIC-Umeå, EPIC-Netherlands, EPIC-Turin and EPIC-San Sebastian had no information on changes of residence during follow-up.

[3] Cochran test for heterogeneity

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Figure 1

150x158mm (250 x 250 DPI)

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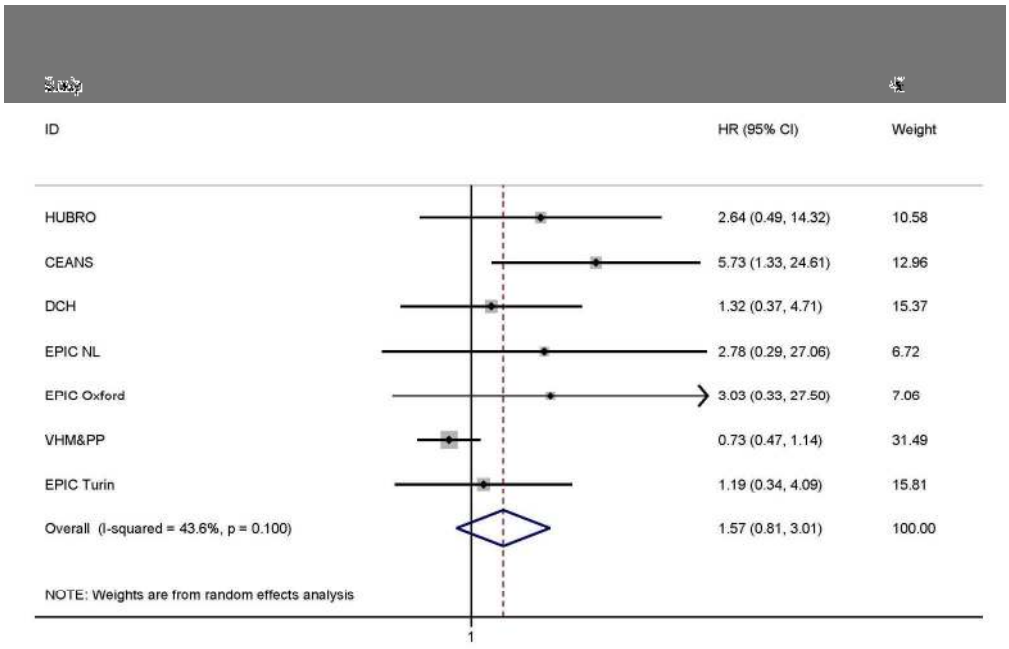

Figure 2 upper panel

272x185mm (200 x 200 DPI)

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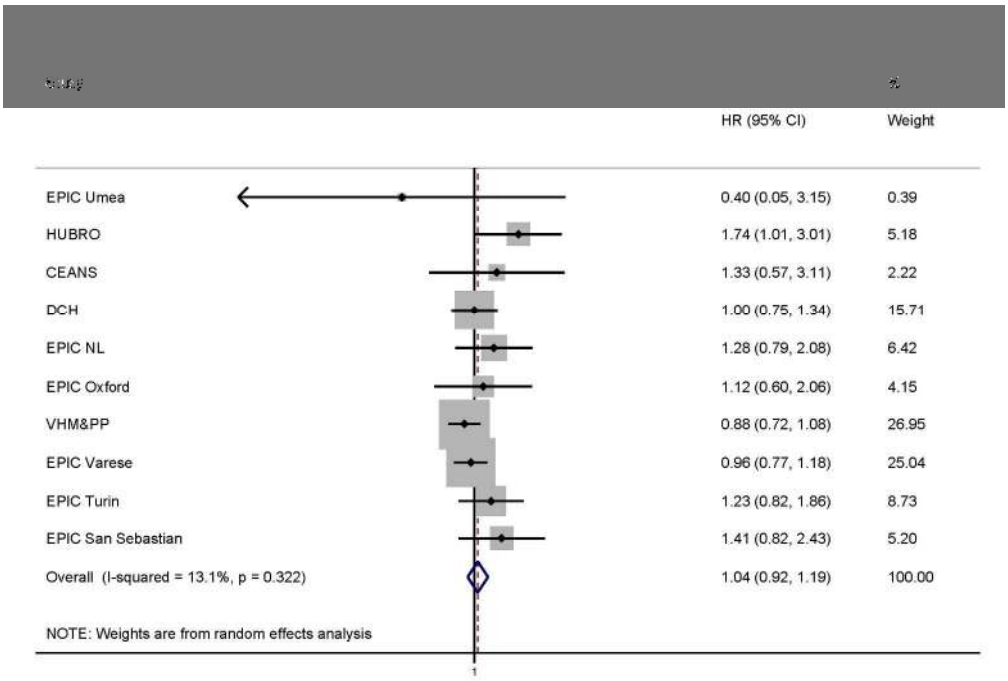

Figure 2 lower panel NO2

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