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Long-term exposure to air pollution and chronic kidney disease-associated mortality–Results from the pooled cohort of the European multicentre ELAPSE-study

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ABSTRACT

Despite the known link between air pollution and cause-specific mortality, its relation to chronic kidney disease (CKD)-associated mortality is understudied. Therefore, we investigated the association between long-term exposure to air pollution and CKD-related mortality in a large multicentre population-based European cohort.

Cohort data were linked to local mortality registry data. CKD-death was defined as ICD10 codes N18–N19 or corresponding ICD9 codes. Mean annual exposure at participant's home address was determined with fine spatial resolution exposure models for nitrogen dioxide (NO_2), black carbon (BC), ozone (O_3), particulate matter $\leq$2.5 μm ($PM_{2.5}$) and several elemental constituents of $PM_{2.5}$. Cox regression models were adjusted for age, sex, cohort, calendar year of recruitment, smoking status, marital status, employment status and neighbourhood mean income.

Over a mean follow-up time of 20.4 years, 313 of 289,564 persons died from CKD. Associations were positive for $PM_{2.5}$ (hazard ratio (HR) with 95% confidence interval (CI) of 1.31 (1.03–1.66) per 5 $\mu g/m^3$, BC (1.26 (1.03–1.53) per 0.5 $\times$ 10^{-5}/m), NO_2 (1.13 (0.93–1.38) per 10 $\mu g/m^3$) and inverse for O_3 (0.71 (0.54–0.93) per 10 $\mu g/m^3$). Results were robust to further covariate adjustment. Exclusion of the largest sub-cohort contributing 226 cases, led to null associations. Among the elemental constituents, Cu, Fe, K, Ni, S and Zn, representing different sources including traffic, biomass and oil burning and secondary pollutants, were associated with CKD-related mortality.

In conclusion, our results suggest an association between air pollution from different sources and CKD-related mortality.

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Ethical approval

Medical ethics committees had approved all cohort studies in their respective countries (CEANS: Regional Ethical Review Board at Karolinska Institutet; DCH: The science-ethical committee for Copenhagen and Frederiksberg municipalities; DNC: The science-ethical committee for Copenhagen and Frederiksberg municipalities Danish Data Protection Agency; EPIC-NL: Medisch Ethische Commissie TNO, Leiden; E3N: Comission Nationale de l'Informatique et des Libertés (CNIL); VHM&PP: Ethikkommisssion Vorarlberg). Anonymized data were transferred to a secure Utrecht University server to build the data set of the pooled cohort.

1. Introduction

Chronic kidney disease (CKD) mortality has become one of the leading causes of death worldwide (GBD, 2013 Mortality and Causes of Death Collaborators, 2015). By 2017 CKD had become the 12th leading cause of death with 1.2 million deaths globally and is expected to reach the 5th rank by 2040 (Bikbov et al., 2020; Kovesdy, 2022).

The CKD risk factors considered in the Global Burden of Disease study were impaired fasting plasma glucose, high blood pressure, high body-mass index (BMI), a diet high in sodium, and lead (Bikbov et al., 2020). Air pollution, which emerges as a relevant risk factor for CKD, was not considered. However, this may be an important oversight because air pollution may also influence the two most important CKD risk factors, glucose tolerance and blood pressure (Brook et al., 2018).

Evidence on the association between air pollution and kidney disease has accumulated over the past years. Previous research showed positive associations with particulate matter (PM) of aerodynamic diameter less than 10 μm (PM_{10}), less than 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) (Wu et al., 2020; Ye et al., 2021). Fewer studies, with conflicting results are available for black carbon (BC, a measure of soot) (Chen et al., 2023; Feng et al., 2021; Xu et al., 2022) and ozone (O_3) (Hwang et al., 2021; Li et al., 2022b; Yang et al., 2022).

The epidemiological evidence has been accompanied by conceptual and toxicological work that indicates that several interlinked systemic pathways progressively damage the nephrons (Shubham et al., 2022). Diverse mechanisms known from cardiovascular and metabolic disease, especially diabetes, seem to play a role - in particular inflammation and oxidative stress. In addition, the above diseases are well-known important risk factors for CKD. Besides initiating CKD, air pollution may also influence prognosis by accelerating CKD progression towards end stage kidney disease (Bowe et al., 2018) and finally CKD-related mortality (Chen et al., 2023; Hu et al., 2023; Ran et al., 2020).

While the effect of air pollution on kidney function and its association with CKD incidence have been increasingly studied, studies on CKD-associated mortality are rare. Bowe et al. estimated the excess burden of CKD-related mortality in the US to be over 7000 deaths, more than ten times as much as the burden related to COPD (Bowe et al., 2019). Nevertheless, results from different studies from different parts of the world are inconsistent (Brauer et al., 2022; Ran et al., 2020; So et al., 2022).

PM constitutes a complex mixture of particles of different size and chemical composition depending on sources and location and this may lead to conflicting results from different study locations. Still, little is known on which sources and elemental constituents or compounds are most crucial to human health.

We therefore investigate the relation of CKD-associated mortality with long-term exposure to different air pollution components in a large European study including population-based cohorts from several countries. Namely, we investigate the association with $PM_{2.5}$, NO_2, BC, O_3 and eight elemental constituents of $PM_{2.5}$ that are indicative of different PM sources.

2. Methods

2.1. Study population

From the pooled cohort of the Effects of Low levels of Air Pollution – a Study in Europe (ELAPSE) we included all subcohorts with at least 10 cases of CKD-associated mortality, namely the Diet, Cancer and Health cohort from Denmark [DCH (Tjønneland et al., 2007),], Danish Nurse Cohort [DNC-1993 (Hundrup et al., 2012),], the prospective sub-cohort of Dutch European Investigation into Cancer and Nutrition [EPIC_NL-Prospect (Beulens et al., 2010),], Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale [E3N from France, (Clavel-Chapelon F, E3N Study Group for the ES,

2015)] and Vorarlberg Health Monitoring and Prevention Programme [VHM&PP from Austria (Ulmer et al., 2007),].

Recruitment of study participants was mostly done in the 1990s and 2000s and information on potential confounders was collected at baseline. Detailed information on the cohorts is provided in (Hvidtfeldt et al., 2021; Strak et al., 2021). Medical ethics committees in the respective countries approved all cohort studies.

2.2. Exposure assessment

We determined the concentrations of air pollutants at the baseline home address with land use regression (LUR) models: for $PM_{2.5}$ and several elemental constituents thereof, NO_2 and BC the annual mean and for O_3 the mean over the warm period i.e. April to September of the year 2010. $PM_{2.5}$ elemental constituents were chosen to represent different sources of PM: copper (Cu), iron (Fe) and zinc (Zn) for (non-tailpipe) traffic emissions, sulfur (S) for long-range transport, nickel (Ni) and vanadium (V) for mixed oil burning/industry, silicon (Si) for crustal material, and potassium (K) for biomass burning (Viana et al., 2008).

LUR models were developed for Western Europe and validated as described in detail in (de Hoogh et al., 2018). In short, the models were created with supervised linear regression using 2010 European Environment Agency (EEA) AirBase routine monitoring data for $PM_{2.5}$, NO_2 and O_3, and monitoring data from the European Study of cohorts on air pollution effects (ESCAPE) for BC and $PM_{2.5}$ elemental constituents (Chen et al., 2020; de Hoogh et al., 2018). In addition to land use and traffic variables, chemical transport model (CTM) estimates and satellite observations were used as potential predictor variables. For $PM_{2.5}$ elemental constituents, information on relevant sources (e.g. industries emitting specific aerosols such as Cu, Ni or Zn) was also incorporated. Exposure values were estimated at participants' home address at baseline with a resolution of 100m × 100m. LUR model performance in fivefold hold-out validation was good, explaining 66 %, 58 %, 51 %, and 60 % of the measured spatial variation for $PM_{2.5}$, NO_2, BC, and O_3, respectively (de Hoogh et al., 2018).

We also performed back-extrapolation of exposure concentrations for $PM_{2.5}$, NO_2, BC, and O_3 using historical pollution data from the Danish Eulerian Hemispheric Model (DEHM) that covers the whole of Europe (Brandt et al., 2012), based either on the ratio or the difference in concentrations between years (for a detailed description see (Brunekreef et al., 2021; Stafoggia et al., 2022)).

2.3. Outcome

Mortality data was derived from mortality registries using the International Classification of Diseases (ICD) codes 9th and 10th revision. CKD-related death was defined as underlying cause of death from death certificates coded by ICD-10 codes N18 (CKD, 585 in ICD-9) or N19 (unspecified kidney failure, 586 in ICD-9). Mortality follow-up started between 1985 and 2005 and ended between 2011 and 2017 depending on the respective cohort (see Table 1).

2.4. Statistical analyses

Cox Proportional Hazard models were used to calculate hazard ratios (HRs) for the association between air pollution and CKD-related mortality. Individuals were censored at the time of death from other causes, emigration, loss to follow-up, or the end of follow-up.

Adjustment models were chosen *a priori* with increasing level of adjustment: Model 1 included age (as timescale), calendar year of enrolment and stratification by cohort and by binary sex. Model 2 was further adjusted for individual-level variables on smoking status (never; former; current), marital status (single; married or living with partner; divorced or separated; widowed) and employment status (yes; no). These individual variables related to the baseline year. Model 3, defined as the main model, adjusted in addition for area-level socio-economic

Table 1
Description of study population.

Cohort	Size of the study population [a] (N)	Individuals in Model 3 (N)	Recruitment period (Baseline)	Years of follow-up (Mean) [b]	CKD mort cases 9 (N)	Crude mortality rate per 100,000 pyears	Age at baseline (mean ± SD)	Female 13 (%)	Current smokers (%)	Employed/Self-employed (%)	Married/17 living with partner (%)	Neighbourhood income [c] (Mean ± SD)
Pooled cohort	315,937	289,564	-	20.44	313	5.29	48.4 ± 13.5	68	25	70	72	19.6 ± 5.1
DCH	56,308	54,658	1993–1997	18.17	35	3.53	56.7 ± 4.4	52	36	78	72	20.2 ± 3.4
DNC-1993	19,664	18,033	1993	18.58	22	6.57	56.5 ± 8.7	100	38	69	67	19.2 ± 2.6
E3N	53,521	51,277	1989–1991	16.68	10	1.17	53.0 ± 6.8	100	13	68	83	11.2 ± 3.1
EPIC_NL-Prospect	16,194	15,205	1993–1997	16.43	20	8.01	57.7 ± 6.1	100	823	51	77	13.1 ± 1.4
VHM&PP	170,250	150,391	1985–2005	23.18	226	6.48	42.0 ± 14.9	56	23	70	69	22.9 ± 1.7

[a] Number of individuals included in the pooled cohort on the Utrecht University server in the cohorts of interest..
[b] From this column on, only for persons in Model 3. CKD: chronic kidney disease.
[c] In Euros × 1,000, year 2001. pyears = person years.

status (SES) using neighbourhood or municipal level mean income in the year 2001 (in 1000€), referred to a neighbourhood-level from hereon. Only individuals without missing covariates in model 3 were included in the analysis.

The proportional hazard assumption was examined by plotting scaled Schoenfeld residuals over time and tested for deviation of the slope from zero. In a sensitivity analyses, variables violating the proportional hazard assumption were included as stratum.

Concentration-response shapes for $PM_{2.5}$, NO_2, BC and O_3 were investigated with natural cubic splines (3 degrees of freedom), subsets (individuals living below a certain concentration) and threshold analyses (exposure variable set to zero below a certain cut-off value and performance evaluated with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) – see online supplement for details.

In sensitivity analyses additional adjustment models included further covariates: BMI (categorical with cut-off points at 18.5 and 24.9 kg/m^2) acknowledging that BMI may be a mediator on the pathway rather than a confounder; smoking intensity (linear, and squared) and smoking duration (continuously in years); level of education (primary school or less; up to secondary school or equivalent; university degree or more); normalized difference vegetation index (mean within 300 × 300m, scale from −100 000 to 100,000) and urban neighbourhood (cities and densely populated areas; towns and suburbs; rural areas, from Eurostat degree of urbanization dataset). As alternative neighbourhood SES indicators we investigated neighbourhood unemployment rate and neighbourhood low education (instead of mean income) as well as neighbourhood ethnicity (in addition to mean income).

We excluded one cohort at a time from model 3 to evaluate the impact of influential cohorts and cohort specific HRs were calculated, also. For $PM_{2.5}$, NO_2, BC and O_3, we also ran model 3 with exposure values back-extrapolated to baseline year and with time-varying exposures considering residential history and respective neighbourhood indicators. Furthermore, two pollutant-models including two of the main pollutants or adjusting the PM-constituents with $PM_{2.5}$ and NO_2, respectively, were calculated. The adjustment for NO_2 was attempted to evaluate potential effects of non-tailpipe emissions from traffic, with Fe and Cu as the main indicators (of brake, tyre and road wear). We acknowledge that, because of the high correlation, it is difficult to separate tailpipe and non-tailpipe pollutant. Effect modification was investigated by including an interaction term. For all analyses, R (version 3.4.0) was used.

3. Results

3.1. Population description

Of 315,937 individuals, 289,564 persons were included in the model 3 dataset, more than half of them from the VHM&PP cohort (Table 1). Over an average follow-up period of 20.44 years, 313 persons died from CKD. The mean age at baseline was 48.4 years with VHM&PP being the youngest cohort (mean age 42.0 years vs 53.0–57.7 years in the other cohorts). The cohorts DNC, E3N and EPIC_NL consisted of females only, and in the pooled cohort, there were 68% females. The neighbourhood mean income varied from 11,200 € in E3N to 22,900 € in VHM&PP.

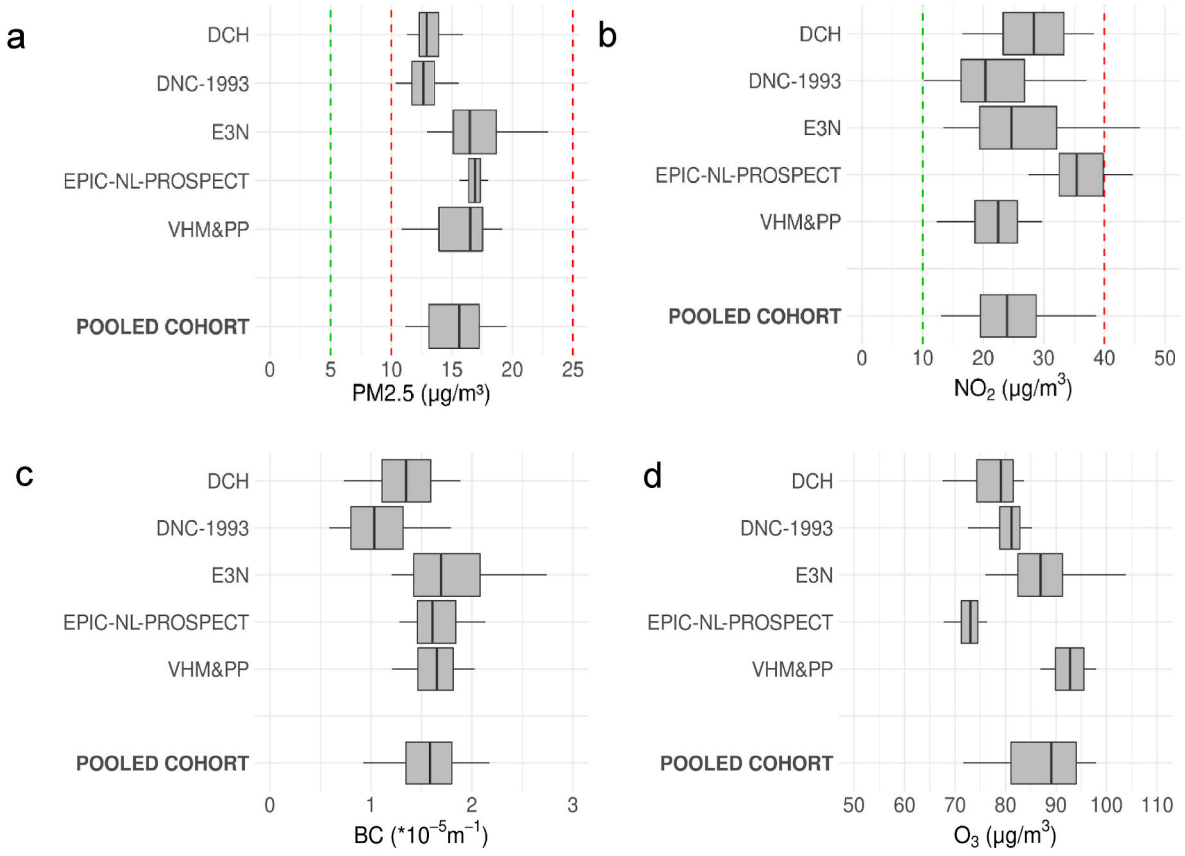

Fig. 1. Exposure to annual mean of a $PM_{2.5}$, b NO_2, c BC and d O_3 (warm season) in 2010 at participants address, per cohort. Data set of model 3 (N = 289,564). Whiskers are for 5th and 95th percentiles. Boundaries of the box are for 25th and 75th percentiles. Bold vertical line is for median. Green = 2021 WHO guidelines 5 and 10 µg/m^3 $PM_{2.5}$ and NO_2, respectively, red = 2005 WHO guidelines 10 and 40 µg/m^3 $PM_{2.5}$ and NO_2, respectively, and EU ambient air quality limit values, 25 and 40 µg/m^3 $PM_{2.5}$ and NO_2, respectively.

3.2. Air pollution description

For $PM_{2.5}$ and BC, exposures in the Danish cohorts (DNC and DCH) were lower than those of the more southern countries (Fig. 1). No similar trend could be observed for NO_2 and O_3. Exposure to $PM_{2.5}$ and NO_2 was below annual limit values ($PM_{2.5}$: 25 μg/m^3; NO_2: 40 μg/m^3) of the European Air Quality Directive (EU-AAQD) for most of the cohorts, but generally above current WHO guidelines for $PM_{2.5}$ (5 μg/m^3) and NO_2 (10 μg/m^3).

Spearman correlation for exposure to air pollution was moderate to high (Supplementary Table S1); especially for BC and NO_2, the correlation was high in every cohort with a median of 0.9 across cohorts, and in the large Vorarlberg cohort correlation of NO_2 and BC with ozone was high.

3.3. Main analyses on the main pollutants

Cox model results showed effect estimates above one for $PM_{2.5}$ and BC (Table 2) e.g. for $PM_{2.5}$ the HR in model 3 was 1.31 (95%CI: 1.03–1.66) for an increase of 5 μg/m^3. Effect estimates for NO_2 were in the same direction, but not statistically significant, e.g. HR of 1.13, 95% CI: 0.93–1.38) per 10 μg/m^3 in model 3. For O_3, statistically significant inverse associations were found.

Natural Splines (Supplementary Fig. S1) were difficult to interpret due to large uncertainties probably due to low number of cases. The same limitation applies to subset and threshold analyses (Supplementary Tables S2 and S3)

In two-pollutant models (Table 3), the effect estimate for $PM_{2.5}$ was stable when adjusting for NO_2, whereas the estimate for NO_2 decreased towards the null. In the model containing $PM_{2.5}$ and BC, the estimates for both decreased moderately, becoming statistically non-significant with widened CIs.

3.4. Elemental constituents

The trend from $PM_{2.5}$ and BC with comparatively small exposure values for the Danish cohorts was continued for most of the $PM_{2.5}$ components (all but Si, and Ni). However, for many components, VHM&PP had low exposure as well, especially for S, Ni, V (Supplementary Fig. S6).

An increased CKD-associated mortality was found for exposure to every $PM_{2.5}$ constituent (see Fig. 2, single models). It was statistically significant for the components representing traffic emissions (Cu, Fe, Zn), biomass burning (K), and long-range transport (S).

In two-pollutant models, adjustment for mass of total $PM_{2.5}$ only slightly changed the effect estimates (Fig. 2). Adjustment with NO_2 increased HRs for Cu and Fe, albeit with very large confidence intervals, with small changes for the other constituents. Note that Spearman correlations of Cu, Fe and Si with NO_2 were high (Fig. 2 legend and Supplementary Table S7).

Table 2
Hazard ratios for the association between air pollution exposure and CKD mortality in the pooled cohort (N = 289,564).

		Model 1[a]	Model 2[b]	Model 3[c]
Pollutant	Increment	HR (95% CI)	HR (95% CI)	HR (95% CI)
$PM_{2.5}$	5 μg/m^3	1.22 (0.96–1.55)	1.22 (0.96–1.54)	1.31 (1.03–1.66)
NO_2	10 μg/m^3	1.04 (0.86–1.25)	1.01 (0.84–1.21)	1.13 (0.93–1.38)
BC	0.5×10^{-5}/m	1.16 (0.96–1.40)	1.13 (0.93–1.36)	1.26 (1.03–1.53)
O_3	10 μg/m^3	0.75 (0.58–0.98)	0.78 (0.60–1.02)	0.71 (0.54–0.93)

HR, hazard ratio; CI, confidence interval; all models were performed on data set for Model 3 where individuals with missing values for any of the Model 3 covariates are excluded.

[a] adjusted for study (strata), sex (strata), age (time axis), calendar year of enrollment..

[b] like Model 1, in addition adjusted for smoking status, marital status, and employment status..

[c] like Model 2, in addition adjusted for neighbourhood mean income in 2001..

3.5. Sensitivity analyses

Effect estimates from the different adjustment models were similar to those of the main analysis (Supplementary Figs. S2 and S3). Only when replacing neighbourhood mean income by neighbourhood unemployment rate and neighbourhood low education, associations attenuated to a certain extent for BC and NO_2, but still with a very large overlap of confidence intervals.

Indications for violation of the proportional hazards assumption were found for smoking status, marital status, employment status and mean neighbourhood income but stratifying for the respective variables showed in general very similar results to the main analysis (Supplementary Table S4). Only when replacing the continuous neighbourhood income by a binary variable categorized with country-specific median as cut-off point the effect estimates attenuated, however regardless of whether this binary variable was included as strata or as covariate.

Excluding one cohort at a time (Supplementary Fig. S4) did not influence the results except for exclusion of the VHM&PP cohort leading to null associations for all pollutants.

Regarding cohort-specific HRs, VHM&PP was the only cohort showing a clear positive association (Supplementary Fig. S5) while the other cohorts showed very large CIs with HRs above and below one due to lower numbers of cases.

Estimates for exposure back-extrapolated to baseline became smaller for $PM_{2.5}$ (Supplementary Table S5) and not statistically significant (ratio method: HR 1.09, 95%CI: 0.98–1.21; difference method: HR 1.05, 95%CI: 0.88–1.26). For BC and NO_2, only small changes were seen and for O_3 the estimates remained the same.

Considering the time-varying exposure led to a mild attenuation for $PM_{2.5}$, strongest in the model with 5-year strata. For BC, NO_2 and O_3, on the contrary, HRs increased moderately with results for NO_2 becoming statistically significant.

4. Discussion

Our study shows a positive association of CKD-related mortality with $PM_{2.5}$ and BC, to a lesser extent with NO_2, and an inverse association with O_3. Results were robust in most sensitivity analyses, but strongly influenced by VHM&PP. VHM&PP is the largest cohort of the analysis that contributed more than half of the included persons and the majority of mortality cases (226 cases) and its omission led to an absence of association. Among the elemental constituents, Cu, Fe, K, Ni, S and Zn, representing different sources, were associated with CKD-related mortality.

Our HR estimate of 1.31 (95% CI: 1.03–1.66) per 5 μg/m^3 increase of $PM_{2.5}$ is similar to that reported for CKD-related mortality by Ran et al., (2020)with a HR of 1.38 (95% CI: 1.09, 1.74) per 5 μg/m^3 in a Hong Kong cohort of older persons (>65yrs). On the other hand, in large cohorts from the entire adult population in Canada and Denmark no association with CKD-related mortality was found (Brauer et al., 2022; So et al., 2022).

Our results for an association between long-term air pollution and CKD-associated mortality are also in line with overall findings for an association with CKD incidence reported by recent meta-analyses (Liu et al., 2020; Wu et al., 2020; Ye et al., 2021), although not directly comparable as the outcome variable mortality in addition to incidence also reflects progression of kidney disease.

For BC, we provide the novel finding of a positive association with CKD mortality. This is in contrast to the seemingly only other study available in the literature, the Danish cohort study by So et al., (2022),

Table 3
Hazard ratios for association between air pollution exposure and CKD mortality. Single- and two-pollutant models, based on Model 3[a] (N = 289,564).

Pollutant	Single-pollutant Model	Two-pollutant Model (Adjusted for pollutants below)			
		$PM_{2.5}$	NO_2	BC	O_3
$PM_{2.5}$	1.31 (1.03–1.66)	NA	1.31 (0.99–1.76)	1.17 (0.86–1.60)	1.16 (0.87–1.55)
NO_2	1.13 (0.93–1.38)	0.99 (0.78–1.26)	NA	0.63[b] (0.40–1.00)	0.88 (0.66–1.18)
BC	1.26 (1.03–1.53)	1.15 (0.89–1.50)	1.92[b] (1.20–3.08)	NA	1.11 (0.83–1.48)
O_3	0.71 (0.54–0.93)	0.78 (0.56–1.09)	0.62 (0.41–0.94)	0.79 (0.53–1.17)	NA

Results are presented as hazard ratio (HR) and 95% confidence interval (CI) for the following increases: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, 0.5 × 10^{-5} m^{-1} for BC and 10 μg/m^3 for O_3.

[a] Adjusted for study (strata), sex (strata), age (time axis), calendar year of enrollment, smoking status, marital status, employment status, and mean income at neighbourhood level in 2001..

[b] Two-pollutant results for BC in combination with NO_2, are difficult to interpret because of their high correlation (Spearman correlation coefficient ≥0.7 in at least three cohorts)..

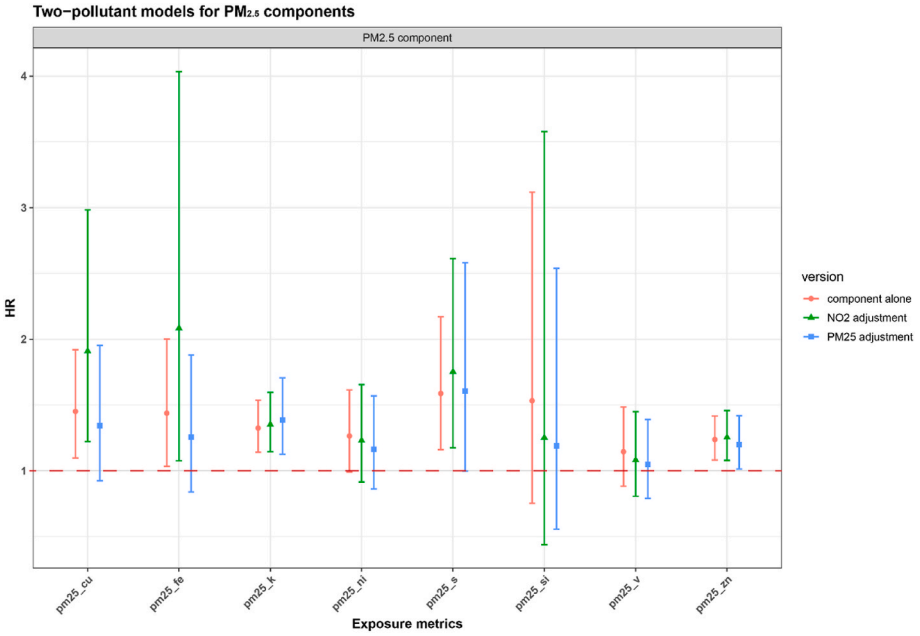

Fig. 2. HRs and 95% CIs between exposure to $PM_{2.5}$ components and CKD mortality in the pooled cohort. Crude and adjusted for NO_2 or $PM_{2.5}$. HRs refer to the following increments:5 ng/m^{3}for $PM_{2.5}$ Cu; 100 ng/m^3 for $PM_{2.5}$ Fe; 50 ng/m^3 for $PM_{2.5}$ K; 1 ng/m^3 for $PM_{2.5}$ Ni; 200 ng/m^3 for $PM_{2.5}$ S; 100 ng/m^3 for $PM_{2.5}$Si; 2 ng/m^3 for $PM_{2.5}$ V; 10 ng/m^3 for $PM_{2.5}$ Zn. Two-pollutant results for Cu, Fe, and Si with NO_2, respectively, are difficult to interpret because of their high correlation (median spearman ≥0.7, i.e. in at least three cohorts).

which, similar to the estimates of the Danish cohorts included in our study (Supplementary Fig. S5), showed no associations with CKD mortality. The few studies on CKD incidence and BC also showed conflicting results (Feng et al., 2021; Xu et al., 2022).

Similarly, studies investigating the relation between NO_2 and CKD mortality are very limited. The Danish cohort found a positive association with a HR of 1.05 (95%-CI: 1.00; 1.11) per 10 μg/m^3 increase (So et al., 2022). This was weaker than our result (HR of 1.13 per 10 μg/m^3, 95%-CI: 0.93–1.38), however with narrower confidence intervals. Both results are in line with a meta-analysis of the association with CKD incidence based on 6 studies (Ye et al., 2021). Two later studies on CKD incidence show either no association (Hwang et al., 2021) or a statistically non-significant one with an increased HR with large confidence intervals (Li et al., 2022b). However, a recent analysis of CKD incidence in UK-Biobank participants free of microvascular disease at baseline (Li et al., 2022a) and in a longitudinal study in Asian children and adolescents (Guo et al., 2022) found statistically significant increased risks of 2% and 7%, respectively.

For ozone, inverse associations have been reported previously (Brauer et al., 2022; Guo et al., 2022; So et al., 2022) but we view our corresponding results critically due to the high correlation with NO_2 and BC, therefore O_3 may rather be a marker of low concentrations of these pollutants, especially in the large Vorarlberg cohort.

Our results show that associations between air pollution and CKD mortality manifest in populations that are exposed to concentrations below the current EU air quality directives (40 μg/m^3 for NO_2, and 25 μg/m^3 for $PM_{2.5}$) and emphasize the need to adapt these thresholds to the current WHO-guidelines. The exact shape of a dose-response curve cannot be reliably inferred from our data, possibly due to a low number of cases especially at the margins of the observed concentrations, and large concomitant uncertainties.

The strength of the associations for all four main pollutants increases after adjustment for small area level mean income. This seems plausible as CKD incidence and progression as well as CKD mortality have been

shown to be influenced by socioeconomic status in general (Fedewa et al., 2014; Fored, 2003; Zeng et al., 2018) and on area-level (Bello et al., 2008), possibly related to differing health care delivery and area-specific living conditions.

We provide novel results on the association between long-term exposure to source related elemental constituents of $PM_{2.5}$ and CKD mortality. To our knowledge, only the Danish administrative cohort (So et al., 2023) has investigated $PM_{2.5}$ constituents and CKD mortality exposures so far.

The three constituents Fe, Cu and Zn, indicating non-exhaust traffic emission, are all associated with CKD mortality in our analysis. The Danish study found an association for Fe and to a lesser extent for Cu, and no association with Zn. Generally there is a lack of studies regarding non-exhaust traffic emission and previous traffic related studies have looked seemingly only at exhaust related traffic emissions (Chen et al., 2018; Hsu et al., 2019; Krauskopf et al., 2018). In the view of a transformation towards increased electric mobility, further studies are clearly needed to disentangle non-exhaust and exhaust traffic pollutants.

Another constituent that may be related to traffic is Si from resuspended road dust. However, it also reflects crustal material from soil in general. We find an elevated HR for Si, however with very large CIs (1.53 (0.75; 3.12)). In the large Danish cohort, So et al. reported a statistically significant positive association (1.077 (1.021, 1.137) supporting our observation (So et al., 2023).

Regarding S, we find a robust relation whereas So et al. found no association (So et al., 2023).

S was chosen to represent long-range transport of secondary PM that is formed in the atmosphere: SO_2 is a precursor of sulphuric acid and sulphates and, after photochemical reaction with organic vapours, of secondary organic aerosols (Kelly and Fussell, 2012).

Sulphates are also related to burning of fossil fuels and were related to combustion of residual oil in a source-apportionment analysis within the ELAPSE project, together with Ni and V that can be considered even more specific markers (Chen et al., 2022b). We do not find any association of CKD-related mortality with V and a positive one for Ni that, however, did not reach statistical significance. Results from the Danish administrative cohort showed a similar pattern, albeit with considerably smaller effect estimates (and more precise CIs) (So et al., 2023).

The strongest and most robust association we observe is for K. This is in clear contrast to the findings in the Danish administrative cohort that found a statistically significant negative i.e. inverse association. K is a tracer for biomass burning and this includes wood, the use of which is very widespread in the Austrian province of Vorarlberg where the large VHM&PP cohort is situated. The VHM&PP cohort has indeed the highest median concentration and clearly the highest exposure contrast among the cohorts. In contrast, the Danish cohorts included in our study have markedly lower concentrations and exposure contrasts, and the same is true for the Danish administrative cohort (So et al., 2023). Under such conditions, detecting an association would be more difficult and may contribute to the difference between the results found here and those in the Danish administrative cohort.

The potential mechanisms underlying the observed associations between air pollution and CKD and its progression to end stage kidney disease have much in common with those in other chronic diseases, especially cardiovascular disease. For the kidney, a highly vascularized organ, oxidative stress and inflammation seem to play a central role. Indeed, the kidney is especially vulnerable to oxidative stress, as reactive oxygen species are important physiological regulators, and it is a highly metabolic organ with high energy demand (Daenen et al., 2019). Correspondingly, mitochondrial dysfunction in relation to oxidative stress seems to be one central mechanism, which can lead to cell apoptosis and cell necrosis and is related to the progression of CKD (Che et al., 2014; Chen et al., 2022a; Daenen et al., 2019; Schlondorff, 2008; Shubham et al., 2022). In the kidney, cell death and loss of podocytes reduces the production of vascular endothelin growth factor leading eventually to endothelial cell apoptosis (Schlondorff, 2008). All these processes compromise the glomerular filtration barrier and thus kidney function.

The direct deposition of $PM_{2.5}$ in the small airways causes pulmonary inflammation. Inflammatory mediators may spill over into the circulation (Brook et al., 2018) and cause harm to distant organs such as the kidneys (Xu et al., 2018). Via this link systemic inflammation may lead to glomerulosclerosis and progressive kidney disease (Shubham et al., 2022). In addition, inflammation leads to a state of hypercoagulability, and emboli within the glomeruli have been suggested to lead to endothelial cell and podocyte damage leading to fibrosis and glomerulosclerosis (Shubham et al., 2022).

Rodent experimental data support a potential causal effect of air pollution on kidney injury. A reduced renal blood flow pointing to renal vascular impairment has been observed in rats exposed to diesel exhaust particles (DEP), with effects potentiated by previous induction of CKD (Suleimani et al., 2017). In another study on mice with CKD, an increase in renal oxidative stress, inflammation and DNA-damage has been observed (Nemmar et al., 2016) upon DEP exposure strengthening a possible link between air pollution and progression of CKD that may eventually lead to premature death.

Our study has several strengths and limitations. First, we could draw on the large database from the ELAPSE pooled cohort with many study participants but also information on many relevant confounders harmonized among individual studies. The analysis of a pooled data set increases our statistical power despite the rather limited number of cases even in this large data set. We cover different areas in Europe including areas with relatively low concentrations, but still can rely on a common exposure assessment according to an advanced state of the art and with a fine spatial resolution. Nevertheless, we had to approximate personal exposure by exposure at the home address. Indeed, in a study of this size it is virtually impossible to obtain personal mobility patterns that may influence exposure to different degrees. However, a study in the Netherlands has shown that effect estimates are rather underestimated as one would expect in the case of non-differential misclassification (Hoek, 2017). Another drawback is that our main exposure assessment relies on annual values for 2010 while recruitment of study participants was earlier. However, in a study of long-term effects, spatial contrasts are the most important and there is evidence that spatial patterns are quite stable over longer time periods (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2013). In addition, our sensitivity analyses using exposure values back-extrapolated to baseline or to the respective years in time-varying analysis, the latter also taking into account changes in address, indicate that the results are overall stable.

We acknowledge the limitation of using LUR models to assess elemental exposure, primarily because of limited availability of specific fine scale predictors of certain elements, e.g. we do not have fine-resolution predictors separating tailpipe and non-tailpipe emissions or wood-burning. Still we entered source-specific predictors from satellite and CTM where possible and, on average, the components models performed similarly to the models of the main pollutants (as judged by the R^2), with differences between the components.

A certain caveat is that the associations are sensitive to exclusion of the largest cohort which contributes by far the most cases and therefore contributes quite precise effect estimates whereas the CIs of all the other studies were generally very large with a large overlap with those of the VHM&PP cohort. Because the Vorarlberg cohort is relatively young compared to the others, and thus in comparison less cases may have been observed, there may be a certain underestimation of the true association. On the other hand, it is the cohort with the longest time of follow-up. In addition, our pooled cohort included 68% females (with three female cohorts of five) which again might have led to a certain underestimate of the association as we observed stronger associations in male individuals.

There are not enough routine monitors in the Vorarlberg region to evaluate how well the models represent the spatial variation of long-term averages. The only data with a sufficient number of monitors

that are available so far are those from the ESCAPE measurement campaign conducted at 20 $PM_{2.5}$ and 40 NO_2 sites. The ELAPSE model explained 22.4% and 47% of the variance for $PM_{2.5}$ and NO_2 respectively. The lower explained variance for $PM_{2.5}$ probably relates to the smaller variability between measurement sites. These R^2 values represent a lower estimate of the agreement, as at each site, measurements were made for three periods of 14 days spread over a year. Hence, the measured ESCAPE average includes temporal variation. It has to be acknowledged that the ESCAPE monitoring area only covered part of the ELAPSE population, notably those living below 600 m of altitude i.e. in the main valley.

Another limitation is that, although we investigated primary underlying causes of death, coding may still lead to cases that have died of kidney failure but as a consequence of other underlying causes. This degree of misclassification may differ between countries and lead to different associations with air pollution. In addition, we cannot exclude that misclassification may lead to an observed association that reflects the air pollution association with all-cause natural mortality, rather than with specific CKD-related deaths. Nevertheless, our HR for BC is overall similar to that for $PM_{2.5}$ whereas for natural mortality it was moderately lower (Strak et al., 2021). However, given the uncertainties around our effect estimates this might be a spurious result. Nevertheless, while we seem to have a similar effect modification by sex with higher HRs in men (Supplementary Table S8), findings for age and smoking were seemingly different to those for natural mortality. This may strengthen the evidence for an association independent of that for natural mortality, however bearing in mind uncertainties due to the low numbers of cases per stratum.

In conclusion, our finding suggest an association of air pollution, related to different sources, with CKD-related mortality, which needs to be confirmed in other studies.

Disclosure statement

The authors declare they have nothing to disclose.

CRediT authorship contribution statement

Pauline Kadelbach: Writing – original draft, Formal analysis. **Gudrun Weinmayr:** Writing – original draft, Formal analysis, Conceptualization. **Jie Chen:** Formal analysis, Data curation. **Andrea Jaensch:** Writing – review & editing, Formal analysis. **Sophia Rodopoulou:** Formal analysis. **Maciej Strak:** Data curation. **Kees de Hoogh:** Data curation. **Zorana J. Andersen:** Writing – review & editing. **Tom Bellander:** Writing – review & editing. **Jørgen Brandt:** Data curation. **Giulia Cesaroni:** Writing – review & editing. **Daniela Fecht:** Writing – review & editing. **Francesco Forastiere:** Writing – review & editing. **John Gulliver:** Writing – review & editing. **Ole Hertel:** Writing – review & editing. **Barbara Hoffmann:** Writing – review & editing. **Ulla Arthur Hvidtfeldt:** Writing – review & editing. **Klea Katsouyanni:** Methodology. **Matthias Ketzel:** Writing – review & editing. **Karin Leander:** Writing – review & editing. **Petter Ljungman:** Writing – review & editing. **Patrik K.E. Magnusson:** Writing – review & editing. **Göran Pershagen:** Writing – review & editing. **Debora Rizzuto:** Writing – review & editing. **Evangelia Samoli:** Methodology. **Gianluca Severi:** Writing – review & editing. **Massimo Stafoggia:** Methodology. **Anne Tjønneland:** Writing – review & editing. **Roel Vermeulen:** Writing – review & editing. **Annette Peters:** Writing – review & editing. **Kathrin Wolf:** Methodology. **Ole Raaschou-Nielsen:** Writing – review & editing. **Bert Brunekreef:** Investigation, Funding acquisition, Data curation. **Gerard Hoek:** Investigation, Funding acquisition, Data curation. **Emanuel Zitt:** Writing – review & editing. **Gabriele Nagel:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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.

Data availability

The exposure maps are available on request. The ELAPSE study protocol is available at http://www.elapseproject.eu/. Further information is available from the corresponding author upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118942.

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