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Particulate air pollution from different sources and mortality in 7.5 million adults — The Dutch Environmental Longitudinal Study (DUELS)☆

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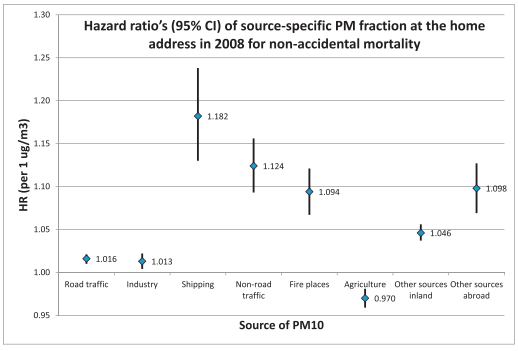
HIGHLIGHTS

- Associations between particulate air pollution from different sources and all-cause mortality were evaluated.
- Associations were found between total and primary particulate matter (PM10 and PM2.5), elemental carbon and mortality.
- Secondary inorganic aerosol showed less consistent associations compared to primary PM and EC.
- PM sources were associated with mortality, except agricultural and, depending on the fraction, industrial PM emissions.
- eNo specific source category of particulate air pollution could be identified as main determinant of the mortality effects.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Long-term exposure to particulate air pollution has been associated with mortality in urban cohort studies. Few studies have investigated the association between emission contributions from different particle sources and mortality in large-scale population registries, including non-urban populations.
Objectives: The aim of the study was to evaluate the associations between long-term exposure to particulate air pollution from different source categories and non-accidental mortality in the Netherlands based on existing national databases.
Methods: We used existing Dutch national databases on mortality, individual characteristics, residence history, neighbourhood characteristics and modelled air pollution concentrations from different sources and air pollution components: particulate matter PM10, primary particulate matter PM10 (PPM10), particulate matter PM2.5, primary particulate matter PM2.5 (PPM2.5), elemental carbon (EC), nitrogen dioxide (NO_2) and secondary inorganic aerosol (SIA) in PM10 (SIA10) or in PM2.5 (SIA2.5). We established a cohort of 7.5 million individuals 30 years or older. We followed the cohort for eight years (2008–2015). We applied Cox proportional hazard regression models adjusting for potential individual and area-specific confounders.
Results: We found statistically significant associations between total and primary particulate matter (PM10 and

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PM2.5), elemental carbon and mortality. Adjustment for nitrogen dioxide did not change the associations. Secondary inorganic aerosol showed less consistent associations. All primary PM sources were associated with mortality, except agricultural emissions and, depending on the statistical model, industrial PM emissions.
Conclusions: We could not identify one or more specific source categories of particulate air pollution as main determinants of the mortality effects found in this and in a previous study. This suggests that present policy measures should be focussed on the wider spectrum of air pollution sources instead of on specific sources.

1. Introduction

Long-term exposure to air pollution has been associated with mortality in several cohort studies (Abbey et al., 1999; Atkinson et al., 2016; Beelen et al., 2014; Brunekreef et al., 2009; Carey et al., 2013; Cesaroni et al., 2013; Chen et al., 2013; Crouse et al., 2012; Di et al., 2017; Dockery et al., 1993; Faustini et al., 2014; Fischer et al., 2015; Hales et al., 2012; Hoek et al., 2013; Huss et al., 2010; Pope 3rd et al., 1995; Ruckerl et al., 2011; Turner et al., 2016; Villeneuve et al., 2015; WHO, 2013; Yap et al., 2012; Yin et al., 2017; Zeger et al., 2008).

Cohort studies specifically designed for investigating individual risk factors are time consuming, labour intensive, often limited in size, and relatively costly. To overcome these disadvantages recent studies have linked existing national databases of air pollution, non-accidental mortality, individual characteristics, and residential history to assess the relationships between air pollution and mortality more efficiently (Carey et al., 2013; Cesaroni et al., 2013; Chen et al., 2013; Crouse et al., 2012; Di et al., 2017; Fischer et al., 2015; Hales et al., 2012; Huss et al., 2010; Villeneuve et al., 2015; Zeger et al., 2008).

Most research on the health effects of air pollution focused on mass concentration of particulate or gaseous components. In a previous study on the health effects of air pollution on mortality in the Netherlands, we found significant associations between long-term estimates of PM10 and NO_2 levels at the home address of 7.1 million members of a registration cohort and non-accidental total mortality and cardiovascular, respiratory, and lung cancer mortality (Fischer et al., 2015). However, the sources of air pollutants most responsible for these adverse health effects are not known yet, limiting the ability to address an effective health related air pollution abatement policy. The National Academy of Sciences (NAS), the WHO and the American Heart Association have placed a high priority on determining which constituents and components of the PM mass are most responsible for these reported health effects (Brook et al., 2010; NRC, 2001; WHO, 2007). If some PM sources are per mass concentration more harmful than others, this could lead to more targeted and cost-effective regulations to protect public health. In the Netherlands, there is an extensive emission registration and yearly maps of air pollution concentrations are produced based on these national and foreign registrations. Since the national registration allows the production of source specific maps, we explored whether linking the data from various national registered source categories could give insight in the harmfulness of PM originating from different sources. The aim of this explorative study was to evaluate the toxicity of long-term exposure to source-related PM with non-accidental mortality in a cohort of 7.5 million Dutch residents.

2. Methods

2.1. The study cohort

The selection of a study cohort has been described elsewhere (Fischer et al., 2015). In short, in the Netherlands population statistics are compiled by Statistics Netherlands (http://www.cbs.nl/en-GB/menu/home/default.htm) and are based on digital municipal population registers (Prins, 2000). This registration system is known as the GBA (Gemeentelijke Basis Administratie), the municipal basic registration of population data. Statistics Netherlands combines the data from the GBA into a longitudinal file for each individual registered in the GBA (de Bruin et al., 2004). These records start on 1-1-1995. Changes in demographic attributes (e.g. death, address, marital status, emigration) are updated on a daily basis. For this study we selected all Dutch inhabitants of 30 years or older on 1-1-2008, living at the same residential address since 1-1-2003 and data about gender, age, marital status, and region of origin. Furthermore, we enriched this selection with standardised disposable household income. This individual socio economic indicator is adjusted for differences in household size and composition.

We also used a social status indicator for 4-digit postcode areas, which comprise on average about 4000 inhabitants. Each postcode area receives a unique ranking between 0 and 1 for social status according to the income level, unemployment rate and education level of its inhabitants, with 1 being the lowest possible ranking on social status within the Netherlands (Knol, 1998). We took the indicator of 2006, or 2010 when 2006 data were missing and linked it to the cohort by the postcode of the residential addresses. We categorized the study population into quintiles of the area social economic class ranking.

The follow up period of the cohort was from 1 to 1-2008 to 1-1-2016 (8 years). Subjects were lost to follow-up if their final record in the longitudinal file ended before 1-1-2016 and death was not registered as a reason for termination. Emigration was the main cause of censoring other than death.

All our analyses were performed within strict privacy rules, i.e. only researchers who received a signed permit were allowed to do analyses using the non-public data within a secured remote access environment of Statistics Netherlands. Prior to publication, Statistics Netherlands made sure that none of the analysis results were traceable to an individual cohort member.

2.2. Mortality outcomes

A database with non-accidental mortality data (ICD-10: A–R) was available from Statistics Netherlands (Harteloh et al., 2010). It has been shown that within the Netherlands differences in regional mortality rates exist, with relatively lower rates in the western part of the country and relatively higher rates in the eastern part. Exact reasons for these differences still remain unknown (Mackenbach, 1992), but as these 'natural' differences may bias the associations between air pollution and mortality, we took these differences in 'frailty' into account in our statistical analyses. We used province (NUTS-2 level) as (administrative) unit for the random effect in the Cox proportional hazards regression models.

2.3. Air pollution exposure assessment

Annual air pollution was calculated for every address in the Netherlands in two stages for the year 2008. The basis is a 1×1 km map (Velders et al., 2017). Input to this map are emissions of all relevant sources and many different components. National emissions are extracted from the National Emission Registration (Jimmink et al., 2016). Emissions from neighbouring countries are extracted from the CLRTAP data base (http://www.ceip.at/webdab_emepdatabase/reported_emissiondata). All these emissions are feed into a dispersion model OPS (van Jaarsveld and de Leeuw, 1993; van Jaarsveld, 2004) yielding grids of concentrations for 100 combinations of components and

sources. The calculated concentrations are calibrated with the observations from the Dutch Air Quality Monitoring Network. The overall uncertainty in the maps is therefore based on the uncertainty in the measured concentrations of about 15% (1 sigma). Every year the modelled concentrations of all air pollutants are compared with the measurements and in general agree well (Velders et al., 2017). Condensables are not taken into account in the PM emissions from especially biomass burning. Implicitly, the contribution from condensables to the total PM concentration is taken into account in the calibration of the total PM concentrations. EC concentrations are based on reported emission ratios EC/PM2.5 for each type of source.

In traffic situations the local contribution of NOx, primary PM10 and PM2.5 and EC are added to the background grids at a much higher resolution using dedicated models (Rutledge-Jonker et al., 2018). Double accounting of highway contributions is prevented by discarding these specific contributions from the background. In routine operation the grids and local contributions are summed to calculate the total concentrations of PM10, PM2.5 and NO_2 for the official Dutch assessment of air quality compliance on approximately 300.000 locations. Both background and traffic contribution results are intensely validated over the years by using thousands of measurement data. The measurement data are also used to recalibrate the model results if necessary (Wesseling et al., 2016).

We clustered the air pollution source contributions into eight categories based on the main source categories and similarity of air pollution profiles resulting from each source type. These profiles were calculated as the percentage of the concentration of EC, PPM10, SIA10, or NO_2 of the sum of the total PPM10, SIA10 and NO_2 concentrations. Table 1 in the Supplement shows the main and sub-categories and the qualitative overall profile for the main categories. Main categories that were selected for analyses were road-traffic, industry, shipping, non-road traffic and other mobile sources, furnaces, agriculture, other sources inland, and other sources abroad (Supplement Table 1). Note that the emissions from tire wear and brakes are included in the road traffic profile. The emissions from these sources are different than those from tail pipes however the dispersion is assumed to be similar.

In the Netherlands secondary inorganic aerosols (SIA) concentrations are relatively high. SIAs are not emitted directly from sources but are the result of atmospheric chemical reactions. Spatial gradients of SIA in the Netherlands are small due to these relatively slow (and partly reversible) formation mechanisms.

2.4. Statistical analyses

Statistical analyses were performed with SAS version 9.4 and SAS/STAT version 13.2 (SAS Institute Inc., Cary, NC). We applied age-stratified (one year strata) Cox-proportional hazards regression models to estimate the associations (hazard ratio, HR, and 95% confidence interval, 95% CI) between mortality and long-term exposure to total modelled concentrations of PM10, PM2.5, NO_2, EC, and SIA and source specific modelled concentrations of primary emissions of PM10, PM2.5 and EC. We analysed the data with adjustment for age and gender, marital status, migration background, household income, and a social status indicator of postcode areas. Unexplained spatial heterogeneity in mortality was addressed by incorporating a frailty variable for the twelve provinces in the Netherlands in the regression model as a random effect. Each Province is an administrative region of about 400,000 to 4 million inhabitants.

2.5. Adjustment for the remainder of the PM mixture

To disentangle the estimated source effect from the total air concentration effect we adjusted the associations between source specific primary emissions of PM10, PM2.5 or EC for the total primary PM10 or PM2.5 levels from all other sources and for the total of same particle size secondary inorganic aerosol. Statistical significant was defined as p-values <.05.

3. Results

On 1-1-2008 the total population of the Netherlands was 16,405,399 of whom 10,497,486 were 30 years of age or older. Of these, 7,530,297 did not move to another address in the previous five years (71.7%) and entered the cohort. Table 1 shows the characteristics of the cohort members on 1-1-2008. During the follow-up period until 1-1-2016 777,148 (10.3%) cohort members died from natural non-accidental causes (Table 1). For the area-specific social economic class variable we observed, as expected, decreasing HR's for total mortality associated with higher social economic class. Also, air pollution levels were slightly inversely correlated with social economic class, with correlation coefficients −0.06 for total NO2, −0.08 for EC and PM2.5, and −0.09 for total PM10. We observed an HR for the highest social economic class versus the lowest class of 0.88 (95% CI: 0.87; 0.89) which appeared invariant with air pollutant and source category.

Table 2 shows mean, range and inter quartile range (IQR) of the modelled air pollution levels in the Netherlands in 2008. Since the last decennium NO_2 levels have decreased with approximately 2–3% per year and PM10 levels decreased on average with 3–4% per year (https://www.researchgate.net/profile/Ronald_Hoogerbrugge/publication/318394243_PM10_en_NO2_concentraties_in_2016_in_lijn_met_dalende_trend/links/5967420b0f7e9b80918576b7/PM10-en-NO2-concentraties-in-2016-in-lijn-met-dalende-trend.pdf?origin=publication_detail).

Average correlations between different modelled PM fractions are relatively high in the Netherlands (Supplement Table 2), about 0.9 for the primary fractions and slightly lower for the secondary inorganic fractions (about 0.7). Correlations between source-specific PM fractions were generally lower (<0.7), with the exception of non-road traffic and other inland sources (Supplement Table 3a–c). Most emissions occur in the western and southern part of the Netherlands, while the eastern and northern regions, which are also less populated, emit far less pollution. As secondary aerosols need some time to form and accumulate in the atmosphere, concentrations are more spread over the country leading to lower correlations with the primary part of PM. The statistical

Table 1
Characteristics of the cohort (N = 7,530,297) at baseline (2008).

Characteristic	Category	Number	(%)
Sex	Male	3,600,886	47.8
	30–40	961,751	12.8
	40–50	1,787,245	23.7
	50–60	1,815,714	24.1
	60–70	1,512,312	20.1
	70–80	933,635	12.4
Age	80+	519,640	6.9
	Married/partnership	5,143,035	68.3
	Single	1,105,500	14.7
	Widowed	659,662	8.8
Marital status	Divorced	622,082	8.3
Mortality	ICD-10 code		
Total Mortality excl. ext. causes	A00-R99	777,148	10.3

Table 2
Modelled air pollution concentrations (mean, range and inter quartile range (IQR)) in μg/m^3 in the Netherlands in 2008.

Air pollutant	Mean	Range	IQR
PM10	25.1	17.3–30.7	2.1
PPM10	4.7	1.4–11.4	1.5
SIA10	6.8	4.5–8.1	0.8
PM2.5	16.6	11.3–21.7	1.6
PPM2.5	3.8	1.3–9.1	1.2
SIA2.5	5.8	3.9–6.8	0.6
EC	1.1	0.3–2.6	0.4
NO2	27.4	10.7–51.0	8.9

consequence of the high correlation between different PM fractions is that it is hard to disentangle which fraction is more relevant than others in the mixture of PM.

The results of the analyses are presented in Table 3. Despite the high correlation between the different pollutants, we choose to present the results from single pollutant models and the results for the models in which we adjusted for the remainder of the aerosol concentration (i.e., the difference between the pollutant level and the total PM concentration) to assess the impact of the adjustment on the single pollutant estimation. All single PM air pollutants show statistically significant associations with non-accidental mortality and the estimated exposures at the home address. Total PM (PM10 or PM2.5) and EC were associated with mortality, as were the primary and secondary inorganic fractions. Per 1 μg/m^3 increase EC shows the highest HR [HR = 1.057 (95% CI: (1.046–1.068)], which is in line with the data presented in a review paper on black carbon (Janssen et al., 2011). Primary particulate matter and secondary inorganic aerosol showed a statistical significant increased risk of 1–2% on mortality per 1 μg/m^3 increase. When EC, primary and secondary fractions associations were adjusted for 'the remainder' of the particle mixture, associations for the secondary aerosol became statistically significant in the opposite direction, while EC associations attenuated but remained significant.

With additional adjustment for NO_2 the estimate for total PM10 decreased by almost 50% and the estimate for primary PM2.5 increased by almost 70% while associations between mortality and EC became statistically insignificant. For other fractions the NO_2 adjustment resulted in minor changes of the estimates.

In Table 4 the associations between mortality and the specific primary PM source contributions are presented. Source specific associations were adjusted for the remaining primary concentration levels and for secondary inorganic aerosol levels in the specific size fraction. All primary particulate source contributions at the home address of the cohort members were statistically significant associated with mortality except source contributions from agricultural activities, which showed negative associations for primary PM10 and PM2.5 emissions and emissions from industry, which showed instable results per fraction with mortality. No stable results could be obtained for EC analyses of the agricultural contribution due to the extremely low emissions of EC compared to the other sources. Relatively high HR's were found for PM from shipping contributions [HR primary PM10 = 1.182 (95% CI: 1.130, 1.238); HR primary PM2.5 = 1.186 (95% CI: 1.131, 1.245); HR EC = 1.465 (95% CI: 1.272, 1.687)], non-road traffic [HR primary PM10 = 1.124 (95% CI: 1.093, 1.156); HR primary PM2.5 = 1.106 (95% CI: 1.072, 1.140), HR EC = 1.193 (95% CI: 1.116, 1.276)] and for furnaces contributions [HR primary PM10 = 1.094 (95% CI: 1.067, 1.121); HR primary PM2.5 = 1.078 (95% CI: 1.050, 1.107); HR EC = 1.44 (95% CI: 1.278, 1.623)], For EC the contribution from other sources abroad showed the highest HR [HR = 2.386 (95% CI: 1.624, 3.507).

Additional adjustment for NO2 did not affect the estimates in a major way (see Supplement Table 3). Adjusting for NO2 does not change the HR-estimates for EC and attenuates the HR-estimates upwards for PPM2.5 of road traffic and shipping and downwards for PPM10 of road traffic. Other estimates for PPM2.5 and PPM10 remained practically unchanged.

4. Discussion

In this explorative study we found statistically significant associations between different fractions of particulate air pollution and non-accidental mortality in a registration cohort of 7.5 million Dutch residents, followed for a period of 8 years during 2008 to 2015. We also found statistically significant associations with a number of source categories of particulate matter. Of eight pre-defined source categories (road traffic, industry, shipping, non-road traffic, furnaces, agriculture, other sources inland, other sources abroad) we found exposures at the home address of the residents to six sources consistently associated with mortality. Exceptions were agriculture, which showed statistical significant associations in the unexpected direction and industry which showed no consistent association with mortality.

Our findings for PM10 are higher than we found in our previous study (Fischer et al., 2015). In our previous study we found an HR of 1.08 per 10 μg/m^3 PM10 (95% CI: 1.07, 1.09) while in the current analyses we find an HR of 1.12 per 10 μg/m^3 PM10 (95% CI: 1.09, 1.14). In our previous analyses we used results of a land use regression model as exposure measure which, in general, result in higher effect estimates due to the finer spatial resolution then with exposure measures based on dispersion modelling based on emission data we used in the current analyses. With our dispersion models we calculated for all sources, except for traffic, concentrations on 1 by 1 km grids, while with the land use regression models and the traffic dispersion models we obtained estimates at the home address. Differences in estimated absolute exposure levels may explain the differences in the effect estimates. Indeed, the median land use regression PM10 estimate in our previous study was 29 μg/m^3 while the current dispersion modelled based estimate is 25 μg/m^3. The percentage mortality in the cohort period was about the same in both studies (9.3% during 7 years follow-up vs 10.3% during 8 years follow-up).

After adjustments for NO_2 the PM10 estimate decreased with 50%, which is in agreement with our previous results. The estimate for PM2.5 however was not affected by NO_2 adjustment.

Table 3
Hazard ratio's (95% CI) per 1 μg/m^3 increase in level of PM fraction at the home address in 2008 for non-accidental mortality.

PM fraction	HR per 1 μg/m^3	Adjusted for other PM	And adjusted for NO_2
PM10	1.011 (1.009–1.013)		1.006 (1.002–1.010)[g]
PM2.5	1.016 (1.013–1.018)		1.015 (1.010–1.021)[g]
EC	1.057 (1.046–1.068)	(10) 1.038 (1.021–1.056)[a]	1.043 (0.992–1.096)
EC		(2.5) 1.017 (0.999–1.036)[b]	1.020 (0.970–1.073)
PPM10	1.015 (1.013–1.018)	1.019 (1.016–1.022)[c]	1.018 (1.012–1.023)[h]
PPM2.5	1.022 (1.019–1.025)	1.026 (1.022–1.030)[d]	1.037 (1.029–1.045)[i]
SIA10	1.013 (1.006–1.019)	0.983 (0.975–0.992)[e]	0.983 (0.975–0.991)[j]
SIA2.5	1.019 (1.011–1.028)	0.983 (0.973–0.993)[f]	0.984 (0.974–0.994)[k]

[a] Adjusted for concentration difference (PM10 – EC) at home address.
[b] Adjusted for concentration difference (PM2.5 – EC) at home address.
[c] Adjusted for concentration SIA10 at the home address.
[d] Adjusted for concentration SIA2.5 at the home address.
[e] Adjusted for concentration PPM10 at the home address.
[f] Adjusted for concentration PPM2.5 at the home address.
[g] PM10 or PM2.5 adjusted for NO_2 at the home address.
[h] 3 adjusted for NO_2 at the home address.
[i] 4 adjusted for NO_2 at the home address.
[j] 5 adjusted for NO_2 at the home address.
[k] 6 adjusted for NO_2 at the home address.

Table 4
Hazard ratio's (95% CI) per 1 μg/m^3 increase in level of source-specific PM fraction at the home address in 2008 for non-accidental mortality,

	PM fraction		
	PPM10[a]	PPM2.5[b]	EC[c]
PM source			
Road traffic	1.016 (1.010–1.021)	1.018 (1.008–1.027)	1.036 (1.016–1.057)
Industry	1.013 (1.004–1.022)	1.001 (0.988–1.014)	0.124 (0.057–0.27)
Shipping	1.182 (1.130–1.238)	1.186 (1.131–1.245)	1.465 (1.272–1.687)
Non-road traffic	1.124 (1.093–1.156)	1.106 (1.072–1.140)	1.193 (1.116–1.276)
Fire places	1.094 (1.067–1.121)	1.078 (1.050–1.107)	1.44 (1.278–1.623)
Agriculture	0.970 (0.959–0.981)	0.801 (0.739–0.867)	
Other sources inland	1.046 (1.037–1.056)	1.057 (1.043–1.071)	
Other sources abroad	1.098 (1.069–1.127)	1.131 (1.093–1.171)	2.386 (1.624–3.507))

[a] Adjusted for difference in total PPM10 concentration minus source specific PPM10 contribution at home address and adjusted for SIA10 concentration at the home address.
[b] Adjusted for difference in total PPM2.5 concentration minus source specific PPM2.5 contribution at home address and adjusted for SIA2.5 concentration at the home address.
[c] Adjusted for difference in total EC concentration minus source specific EC contribution at home address and adjusted for SIA2.5 and PPM2.5 concentration minus source specific EC contribution at the home address.

In the Supplemental material with our previous study (Fischer et al., 2015) we gave an overview of the published literature on mortality and long-term exposure to air pollution. Our current PM10 and PM2.5 results are in qualitative agreement with several other cohort studies (Beelen et al., 2008; Beelen et al., 2014; Carey et al., 2013; Cesaroni et al., 2013; Crouse et al., 2012; Crouse et al., 2015; Di et al., 2017; Hales et al., 2012; Hart et al., 2015; Kioumourtzoglou et al., 2015; Shi et al., 2016; Thurston et al., 2016a; Wang et al., 2016; Zeger et al., 2008). Our PM10 and PM2.5 estimates are at the higher end, although some studies report higher estimates (Hansell et al., 2016; Pinault et al., 2016; Pinault et al., 2017; Wang et al., 2017). Uncertainties in dispersion modelling in combination with an underestimation of the exposure levels may be an explanation for this, but as dispersion models in the Netherlands are continuously validated by measurements and, if applicable, re-calibrated by field measurements, we think that this cannot be the sole explanation. Further studies on the comparability of land use regression models and dispersion models are recommended.

In our study we found both total primary and secondary aerosol to be associated with non-accidental mortality in all one pollutant models. Adjustment for the remainder of the particle mixture changed the associations for secondary aerosol, which seemed to be biased by primary aerosol. Associations with primary aerosol remained statistically significant, also after adjustment for secondary aerosol. Our results therefore suggest that secondary aerosol may not be associated with total mortality in the Netherlands. However, as shown in Supplement Table 2 correlations between different PM fractions were very high and therefore one should be careful in interpreting the multi-pollutant models. We choose to show the impact of the adjustment but, as co-linearity may have unpredicted influences on the effect sizes of the individual fractions, our conclusion concerning secondary aerosol should be further investigated.

PM contributions from six out of the eight predefined primary PM sources were statistically significant associated with non-accidental mortality in the Netherlands. Exposure to industrial primary PM was not associated with mortality while agricultural primary PM was statistically inversely associated with mortality. Primary PM10 and PM2.5 from shipping show the highest HR's, while for EC the contribution from other sources abroad shows the highest HR. The relative higher toxicity of shipping-related PM has been documented before by (Kioumourtzoglou et al., 2015) were they found higher PM2.5 HR's in cities with harbours in the Northwest of the US. These cities were characterized by high nickel and vanadium concentrations, indicating high emissions from heavy fuel oil (bunker fuel) combustion. Unfortunately, we do not have information about the PM composition to test this hypothesis in our study. It remains unknown why, per 1 μg/m^3, primary PM emissions from other sources abroad show such a high HR's. This suggests that primary PM concentrations of unknown, not modelled, sources abroad are much more toxic than known primary PM concentrations of sources from abroad. We do not have an explanation for this.

Road traffic, shipping, furnaces, other sources inland, and other sources abroad all were statistically significant associated with non-accidental mortality in the Netherlands. Despite the urgent call of WHO, the National Research Council and the American Heart Association to place a high priority on determining which constituents and components of the PM mass are most responsible for reported health effects, the number of studies that have looked into source-specific health outcomes is small. In a study in Sweden, which looked into the source-specific effects on cardiovascular disease in two Swedish cohorts (Stockfelt et al., 2017), health effects could not be attributed to specific PM sources. The sources that were separately studied were road traffic exhaust, road traffic non-exhaust (mainly road wear), residential heating, shipping, industry, and other activities (e.g. off-road machinery, agricultural sources). In a study on the effects of different sources on ischemic heart disease (IHD) mortality in the US (Thurston et al., 2016b), two types of sources (coal burning and metal-related sources) out of eight (metals industry, soil particles, motor vehicle traffic, steel industry, coal combustion, oil combustion, salt particles, and biomass burning) showed statistically significant associations with IHD mortality. Although all HR's were > 1 except for biomass burning, none of the remaining six associations reached statistical significance. In a cohort study among female teachers in the State of California, non-accidental mortality and cause-specific mortality were analysed in relation to primary PM2.5 contributions from specific sources (Ostro et al., 2015). Sources investigated were on-road gasoline, off-road gasoline, on-road diesel, off-road diesel, wood smoke, meat cooking, high-sulfur fuel combustion (including distillate oil, marine vessel fuel, aircraft jet fuel, liquid and solid waste fuel), and "other anthropogenic". The only statistically significant association observed between sources and all-cause mortality was for the source of high-sulfur fuel combustion (HR = 1.03; 95% CI: 1.01, 1.05 for a change in its IQR). Although the latter two studies suggest that combustion sources are more important for mortality than other sources, several papers from the European Study of Cohorts for Air Pollution Effects (ESCAPE) indicated no specific constituents of PM particle to be associated with mortality outcomes (Beelen et al., 2015; Raaschou-Nielsen et al., 2016; Wang et al., 2014).

One study has been reported that specifically assessed the relation between PM exposure and mortality in a farmers' cohort (Weichenthal et al., 2014). Although the composition of PM was not analysed, the authors assumed that PM exposure in the study areas (Iowa and North-Carolina) was mainly from rural origin. PM2.5 was not associated with non-accidental mortality in the cohort as a whole, but consistent inverse relationships were observed among women. If indeed the PM mixture was predominantly from rural (or agricultural) origin, the finding is in line with our finding that non-combustion agricultural PM sources showed an inverse association with non-accidental mortality. Although Weichental et al. nor we found an association between non-accidental mortality and exposure to rural or agricultural PM, this does not mean that rural dust is in general not related to health

outcomes. In the Netherlands (a country with large-scale, intensive animal farming, especially in some specific regions), concerns about public health risks of increasingly intensive live-stock farming continue to rise, in particular related to emerging zoonotic infectious diseases such as avian and swine influenza, Q fever (Roest et al., 2011), and pneumonia. Recent studies showed associations with increased pneumonia incidences among residents of animal farms (Freidl et al., 2017; Smit et al., 2012). Local exposure to agricultural PM emissions could be an explanation for these findings. Before giving any meaningful interpretation of the inverse association between PM from agricultural sources and non-accidental mortality, this finding has to be replicated in future studies.

Our results contribute to the evidence linking long-term ambient air pollution exposure to increased non-accidental mortality. We did not identify one specific source that was solely or mainly associated with mortality while other sources were not. Our study has several strengths. The study size is very large and includes all Dutch citizens of 30 years and older in 2008, living at least for five years at the 2008 address which improves the long-term exposure classification. We used address level for all cohort members, based on the annual mean PM10, PM2.5, EC and NO_2 concentrations in 1×1 km grids. For road-traffic contribution we adjusted the grid data with the local influence of main traffic roads on the concentrations at the addresses in the grid in order to obtain more precise concentration estimates. We had individual information about important predictors of mortality at both the individual and postal code levels.

Apart from the strengths, there are also limitations of our study. Exposures were estimated by a dispersion model for the year 2008 and assigned to the cohort for the follow up period 2008–2015. Although the exposure assignment precedes the follow up period, we are not sure that the 2008 annual average adequately represents a longer (historical) exposure window which is relevant for long-term exposure. However there is evidence from the literature that spatial distribution of air pollution is stable over 10-years periods (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2011). Still, people might have moved since 2008 to other addresses and therefore might have changed to another exposure level. Another limitation of the exposure assessment method is that we only assessed outdoor concentrations at the baseline residential address, not taking into account factors related to infiltration of outdoor air pollution into the home such as air exchange rate. Also, we did not have information about the work address, or about the time participants spent at home or about the time commuting in traffic. The resulting misclassification is however likely to be non-differential.

Because of the limited availability of individual life style factors we adjusted for individual and area-level social status, as in the American Cancer Society study, ACS (Krewski et al., 2009) and the European Study of Cohorts for Air Pollution Effects, ESCAPE (Beelen et al., 2014) study. The two confounders represent different 'contextual' environments. Over-adjustment is a possibility, but unlikely, because the correlation between the two covariates is low (0.21).

No information on individual risk factors such as smoking, diet, alcohol use, and body weight was available. In a previous paper we evaluated the possibility whether uncontrolled confounding from life style factors might have biased our results using data from over 60,000 30–65 year old participants of health surveys conducted in 2003–2005 by 11 Community Health Services (Fischer et al., 2015). As we observed associations for the whole exposure distribution we concluded that it was unlikely that uncontrolled confounding from smoking or body weight had substantially biased our results ((Fischer et al., 2015), Supplemental Material Fig. 2 and Tables S1–S4.)

In a second sensitivity analyses we used regional age-standardised smoking attributable mortality fractions, (Janssen and Spriensma, 2012). We found that additional adjustment in the analyses with an area-level proxy for smoking reduces the HRs but did not materially affect the conclusions of the study ((Fischer et al., 2015), Supplemental Material, Table S5). There are several cohorts studies published with missing data on, presumably important individual confounders but most of them showed that relative risk estimates did not materially change when some additional adjustment was made by using proxies for individual risk factors on an aggregated level (Cesaroni et al., 2013; Chen et al., 2013; Villeneuve et al., 2011; Zeger et al., 2008). In general, this suggests that there is evidence that the lack of individual data on smoking and body weight did not bias the results in such a way that conclusions drawn on data with missing information for some individual potential confounders are materially wrong. However, even small associations between air pollution and lifestyle factors may affect the estimates (Strak et al., 2017). We can therefore not exclude that the lack of individual data on smoking and body weight may have biased the results.

5. Conclusions

Based on the results of our explorative study we could not identify one or more specific sources of particulate air pollution as being the main determinants of the mortality effects we have found in this and in previous studies. This suggests that policy measures should be focussed on the wider spectrum of air pollution sources instead of on one or more specific sources.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.135778.

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