Supplementary Appendix

Long-term exposure to low-level air pollution and natural mortality – a pooled analysis of eight European cohorts within the ELAPSE project

Maciej Strak, Ph.D., Gudrun Weinmayr, Ph.D., Sophia Rodopolou, Ph.D., Jie Chen, M.S., Kees de Hoogh, Ph.D., Zorana J. Andersen, Ph.D., Richard Atkinson, Ph.D., Mariska Bauwelinck, M.S., Teresa Bekkevold, M.S., Tom Bellander, Ph.D., Marie-Christine Boutron-Ruault, M.D., Jørgen Brandt, Ph.D., Giulia Cesaroni, M.S., Hans Concin, M.D., Daniela Fecht, Ph.D., Francesco Forastiere, M.D., John Gulliver, Ph.D., Ole Hertel, Ph.D., Barbara Hoffmann, M.D., Ulla Arthur Hvidtfeldt, Ph.D., Nicole A.H. Janssen, Ph.D., Karl-Heinz Jöckel, Ph.D., Jeanette T. Jørgensen, M.S., Matthias Ketzel, Ph.D., Jochem O. Klompmaker, Ph.D., Anton Lager, Ph.D., Karin Leander, Ph.D., Shuo Liu, M.S., Petter Ljungman, M.D., Patrik K.E. Magnusson, Ph.D., Amar J. Mehta, Ph.D., Gabriele Nagel, Ph.D., Bente Oftedal, Ph.D., Göran Pershagen, M.D., Annette Peters, Ph.D., Ole Raaschou-Nielsen, Ph.D., Matteo Renzi, M.S., Debora Rizzuto, Ph.D., Yvonne T. van der Schouw, Ph.D., Sara Schramm, M.D., Gianluca Severi, Ph.D., Torben Sigsgaard, M.D., Mette Sørensen, Ph.D., Massimo Stafoggia, Ph.D., Anne Tjønneland, M.D., W.M. Monique Verschuren, Ph.D., Danielle Vienneau, Ph.D., Kathrin Wolf, Ph.D., Klea Katsouyanni, Ph.D., Bert Brunekreef, Ph.D., Gerard Hoek, Ph.D.,[*] Evangelia Samoli, Ph.D.[*]

[*]these authors contributed equally

Table of contents

Section 1 Characteristics of the included cohorts

Table S1 Study populations

Cohort	Study area	Recruitment	Follow-up until
CEANS-SDPP	Stockholm county, Sweden	1992 – 1998	2011
CEANS-SIXTY		1997 – 1999	2014
CEANS-SALT		1998 – 2002	2011
CEANS-SNACK		2001 – 2004	2011
DCH	Cities of Copenhagen and Aarhus, Denmark	1993 – 1997	2015
DNC-1993	Denmark-wide	1993	2013
DNC-1999		1999	2013
E3N	France-wide	1989 - 1991	2011
EPIC-NL-MORGEN	Four cities, The Netherlands	1993 – 1997	2013
EPIC-NL-PROSPECT		1993 – 1997	2013
HNR	Ruhr area, Germany	2000 – 2003	2015
KORA-S3	Augsburg area, Germany	1994 – 1995	2011
KORA-S4		1999 – 2001	2014
VHM&PP	Vorarlberg region, Austria	1985 – 2005	2014

Table S2 Association of air pollution exposure and covariates

Variable	Level	Total number of observations	PM2.5	NO_2	BC	O_3
Sex	**Female**	214,900	15.1 (2.1)	25.4 (6.7)	1.5 (0.3)	84.9 (4.7)
	Male	110,467	14.8 (2.0)	24.3 (5.7)	1.5 (0.3)	86.1 (4.1)
BMI	**Underweight**	7,499	15.5 (2.4)	24.2 (6.6)	1.6 (0.3)	88.3 (4.7)
	Normal	177,053	15.1 (2.1)	24.8 (6.6)	1.5 (0.3)	85.9 (4.7)
	Overweight	105,287	14.8 (1.9)	25.2 (6.1)	1.5 (0.3)	84.5 (4.3)
	Obese	35,528	15.0 (1.9)	25.6 (6.0)	1.5 (0.3)	84.3 (4.2)
Smoking	**Never smoker**	187,295	15.3 (2.2)	24.0 (6.2)	1.6 (0.3)	87.6 (4.4)
	Former smoker	59,488	14.4 (1.6)	26.6 (6.7)	1.4 (0.3)	80.9 (4.6)
	Current smoker	78,584	14.8 (1.9)	26.1 (6.4)	1.5 (0.3)	83.2 (4.6)
Marital status	**Single**	46,164	15.6 (2.3)	25.9 (6.5)	1.6 (0.3)	85.9 (4.9)
	Married/living with partner	233,418	15.0 (2.0)	24.5 (6.3)	1.5 (0.3)	85.6 (4.4)
	Divorced/separated	27,002	14.6 (1.7)	27.3 (5.9)	1.5 (0.3)	81.7 (4.5)
	Widowed	18,783	14.8 (2.0)	25.2 (5.8)	1.5 (0.3)	85.3 (3.8)
Employ-ment	**No**	97,602	15.3 (2.0)	25.5 (6.1)	1.6 (0.3)	85.2 (4.4)
	Yes	227,765	14.9 (2.1)	24.8 (6.4)	1.5 (0.3)	85.4 (4.5)

Mean (standard deviation) values are reported.

Cohort profile: **CEANS**

Cardiovascular Effects of Air Pollution and Noise in Stockholm

All participants resided in Stockholm County, Sweden. The cohort is comprised of four sub-cohorts: The Stockholm Diabetes Preventive Program (SDPP) is a population-based prospective study of 7,949 subjects aged 35–54 years.[1] The SIXTY subcohort consists of a random population sample of one-third of all men and women living in Stockholm County turning 60 years between August 1997 and March 1999.[2] The Screening Across the Lifespan Twin Study (SALT) sampled 7,043 individuals from the Swedish Twin Register born 1958 and earlier, who lived in Stockholm County.[3] Lastly, The Swedish National Study of Aging and Care in Kungsholmen (SNAC-K) randomly sampled individuals 60+ years of age from a central area in Stockholm.[4]

Variable		Total	CEANS, subcohorts			
			SDPP	SIXTY	SALT	SNAC-K
Baseline year, range		1992–2004	1992–1998	1997–1999	1998–2003	2001–2004
Enrolled, N		21,987	7,835	4,180	6,724	3,248
Included in mortality analyses, N		20,702	7,727	3,969	6,176	2,830
Included in stroke incidence analyses, N		19,805	7,484	3,824	5,944	2,553
Included in lung cancer incidence analyses, N		18,963	7,315	3,663	5,626	2,359
Age at baseline, mean ±SD[a]		56.3±11.4	47.1 ±4.9	60 ±0	57.8 ±10.6	72.9 ±10.4
Women, N (%)		11,979 (58)	4,727 (61)	2,068 (52)	3,417 (55)	1,767 (62)
Unemployed, N (%)		6,367 (31)	711 (9)	1,283 (32)	2,199 (36)	2,174 (77)
Marital status						
	Single	2,776 (13)	1,272 (16)	182 (5)	863 (14)	459 (16)
	Married	14,869 (72)	6,455 (84)	2,933 (74)	4,181 (68)	1,300 (46)
	Divorced	1,731 (8)	-	650 (16)	693 (11)	388 (14)
	Widowed	1,326 (6)	-	204 (5)	439 (7)	683 (24)
Smoking status, N (%)						
	Current	4,592 (22)	2,038 (26)	839 (21)	1,311 (21)	404 (14)
	Previous	7,474 (36)	2,813 (36)	1,523 (38)	2,059 (33)	1,079 (38)
	Never	8,636 (42)	2,876 (37)	1,607 (40)	2,806 (45)	1,347 (48)
Smoking intensity, g/d mean ± SD		13.1 ±7.7	13.5 ±7.4	13.4 ±7.6	12.7 ±8.0	11.7 ±8.2
Smoking duration, yrs mean ±SD		33.6±11.0	27.9 ±8.6	36.3±9.9	37.9 ±9.3	43.3 ±13.6
BMI, kg/m^2						
	< 18.5	252 (1)	54 (1)	26 (1)	94 (2)	78 (3)
	18.5–24.9	9,964 (48)	3,691 (48)	1,398 (35)	3,624 (59)	1,251 (44)
	25.0–29.9	7,971 (39)	3,013 (39)	1,770 (45)	2,054 (33)	1,134 (40)
	30.0+	2,515 (12)	969 (13)	775 (20)	404 (7)	367 (13)
Neighborhood income[b], mean ±SD		25.3±5.6	24.3 ±4.2	24.7 ±6.9	25.3±6.6	28.7 ±2.2

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main references:

- Eriksson AK, Ekbom A, Granath F, *et al*. Psychological distress and risk of pre-diabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women. DiabetMed 2008;25:834–42.
- Wändell PE, Wajngot A, de Faire U, *et al*. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. Diabetes Metab 2007;33:30–6.
- Lichtenstein P, Sullivan PF, Cnattingius S , *et al*. The Swedish Twin Registry in the third millennium: an update. Twin Res Hum Genet 2006;9:875–82.
- Lagergren M, Fratiglioni L, Hallberg IR, *et al*. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clin Exp Res 2004;16:158–68.

Cohort profile: **DCH**

Diet, Cancer and Health

Participants were recruited among persons aged 50-64 years from the areas of greater Copenhagen and Aarhus, Denmark, who were born in Denmark and free of cancer.

Variable		Total
Baseline year, range		1993–1997
Enrolled, N		56,308
Included in mortality analyses, N		53,647
Included in stroke incidence analyses, N		52,088
Included in lung cancer incidence analyses, N		53,647
Age at baseline, mean ±SD[a]		56.7 ± 4.4
Women, N (%)		28,134 (52)
Unemployed, N (%)		11,650 (22)
Marital status		
	Single	3,241 (6)
	Married	38,382 (72)
	Divorced	9,056 (17)
	Widowed	2,968 (6)
Smoking status, N (%)		
	Current	19,459 (36)
	Previous	14,959 (28)
	Never	19,229 (36)
Smoking intensity, g/d mean ±SD		16.4 ± 9.0
Smoking duration, yrs mean ±SD		36.3 ± 7.7
BMI, kg/m^2		
	< 18.5	421 (1)
	18.5–24.9	23,155 (43)
	25.0–29.9	22,311 (42)
	30.0+	7,760 (14)
Municipality level income[b]**, mean ±SD**		20.2 ±3.4

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:

Tjonneland A, Olsen A, Boll K et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scand J Public Health 2007; 35: 432–41

Cohort profile: **DNC**

Danish Nurse Cohort

The cohort was sampled among members of The Danish Nurse Organization (DNO) including both working and retired nurses. Questionnaires were mailed in 1993 to members aged 45+ years and again in 1999 with the inclusion of new members (45+ years).

Variable		Total	DNC, subcohorts	
			DNC-1993	DNC-1999
Baseline year		1993,1997	1993	1999
Enrolled, N		28,433	19,664	8,769
Included in mortality analyses, N		25,171	17,043	8,128
Included in stroke incidence analyses, N		24,865	16,810	8,055
Included in lung cancer incidence analyses, N		23,018	15,581	7,437
Age at baseline, mean ±SD[a]		53.5±8.3	56.2±8.4	47.9 ±4.2
Women, N (%)		25,171 (100)	17043 (100)	8128 (100)
Unemployed, N (%)		5544 (22)	5,116 (30)	428 (5)
Marital status				
	Single	2558 (10)	1799 (11)	759 (9)
	Married	17688 (70)	11527 (68)	6161 (76)
	Divorced	3159 (13)	2115 (12)	1044 (13)
	Widowed	1766 (7)	1602 (9)	164 (2)
Smoking status, N (%)				
	Current	8708 (35)	6383 (37)	2325 (29)
	Previous	7522 (30)	4872 (29)	2650 (33)
	Never	8941 (36)	5788 (34)	3153 (39)
Smoking intensity, g/d mean ±SD		13.7 ±8.0	13.9 ± 8.2	13.3 ±7.3
Smoking duration, yrs mean ±SD		30.4±9.5	31.6 ± 9.9	27.1 ± 7.1
BMI, kg/m^2				
	< 18.5	642 (3)	500 (3)	142 (2)
	18.5–24.9	17,307 (69)	11,760 (69)	5,547 (68)
	25.0–29.9	5,798 (23)	3,899 (23)	1,899 (23)
	30.0+	1,424 (6)	884 (5)	540 (7)
Municipality level income[b], mean ±SD		19.1±2.5	19.2 ±2.6	19.0 ±2.4

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:
Hundrup YA, Simonsen M, Jørgensen T, Obel EB. Cohort profile: The Danish Nurse Cohort. International Journal of Epidemiology, 2012;41:1241–47.

Cohort profile: **EPIC-NL**

European Prospective Investigation into Cancer and Nutrition, The Netherlands

The EPIC-NL combines two Dutch EPIC-cohorts: The Monitoring Project on Risk Factors and chronic diseases in the Netherlands (MORGEN) cohort which consists of a general population sample aged 20–59 years from three Dutch towns (Amsterdam, Doetinchem and Maastricht). Prospect is a prospective cohort study among women aged 49–70, residing in the city of Utrecht or its vicinity, who participated in the nation wide Dutch breast cancer screening programme between 1993 and 1997.

Variable		Total	EPIC-NL, subcohorts	
			MORGEN	PROSPECT
Baseline year		1993–1997	1993–1997	1993–1997
Enrolled, N		36,905	20,711	16,194
Included in mortality analyses, N		32,872	18,302	14,570
Included in stroke incidence analyses, N		31,847	17,643	14,204
Included in lung cancer incidence analyses, N		31,442	17,802	13,640
Age at baseline, mean ± SD[a]		49.5±11.9	42.9± 11.2	57.7±6.1
Women, N (%)		24,630 (75)	10,060 (55)	14,570 (100)
Unemployed, N (%)		12,891 (39)	5,723 (31)	7,168 (49)
Marital status				
	Single	5,468 (17)	4,632 (25)	836 (6)
	Married	23,102 (70)	11,923 (65)	11,179 (77)
	Divorced	2,552 (8)	1,380 (8)	1,172 (8)
	Widowed	1,750 (5)	367 (2)	1,383 (9)
Smoking status, N (%)				
	Current	9,694 (29)	6,359 (35)	3,335 (23)
	Previous	9,950 (30)	5,155 (28)	4,795 (33)
	Never	13,228 (40)	6,788 (37)	6,440 (44)
Smoking intensity, g/d mean ±SD		15.0 ±8.7	15.7 ±8.6	13.7 ±8.7
Smoking duration, yrs mean ±SD		28.9±11.2	24.8 ±10.6	36.8 ±7.6
BMI, kg/m^2				
	< 18.5	275 (1)	188 (1)	87 (1)
	18.5–24.9	15,633 (48)	9,128 (50)	6,505 (45)
	25.0–29.9	12,662 (39)	6,872 (38)	5,790 (40)
	30.0+	4,302 (13)	2,114 (12)	2,188 (15)
Neighborhood income[b], mean ± SD		12.6 ±1.6	12.2 ± 1.6	13.1±1.4

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:
Beulens JWJ, Monninkhof EM, Verschuren WMM et al. Cohort Profile: The EPIC-NL study. International Journal of Epidemiology 2010; 39: 1170–78.

Cohort profile: **HNR**

Heinz Nixdorf Recall study

The cohort consists of randomly sampled persons aged 45 to 75 years from the Ruhr area, Germany primarily in the three adjacent large cities Bochum, Essen, and Mülheim.

Variable		**Total**
Baseline year, range		2000–2003
Enrolled, N		4,809
Included in mortality analyses, N		4,733
Included in stroke incidence analyses, N		4,375
Included in lung cancer incidence analyses, N		3,611
Age at baseline, mean ±SD[a]		59.7±7.8
Women, N (%)		2,382 (50)
Unemployed, N (%)		2,838 (60)
Marital status		
	Single	274 (6)
	Married	3,538 (75)
	Divorced	472 (10)
	Widowed	449 (9)
Smoking status, N (%)		
	Current	1,113 (24)
	Previous	1,619 (34)
	Never	2,001 (42)
Smoking intensity, g/d mean ±SD		18.6 ± 12.0
Smoking duration, yrs mean ±SD		34.5 ± 9.4
BMI, kg/m^2		
	< 18.5	16 (0)
	18.5–24.9	1,237 (26)
	25.0–29.9	2,171 (46)
	30.0+	1,309 (28)
Neighborhood income[b], mean ±SD		25.2 ± 8.2

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:

Schmermund A, Möhlenkamp S, Stang A et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study. American Heart Journal, 2002; 144: 212–2018.

Cohort profile: **E3N**

Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale

The cohort was selected among French women aged 40 to 65 years who were insured through a national health system that primarily covered teachers. The cohort is nation-wide.

Variable		Total
Baseline year, range		1989–1991
Enrolled, N		53,521
Included in mortality analyses, N		39,006
Included in stroke incidence analyses, N		-
Included in lung cancer incidence analyses, N		36,597
Age at baseline, mean ±SD[a]		53.0± 6.8
Women, N (%)		39,006 (100)
Unemployed, N (%)		12,598 (32)
Marital status		
	Single	6,530 (17)
	Married	32,476 (83)
	Divorced	-
	Widowed	-
Smoking status, N (%)		
	Current	5,060 (13)
	Previous	7,500 (19)
	Never	26,446 (68)
Smoking intensity, g/d mean ±SD		11.4 ±9.2
Smoking duration, yrs mean ±SD		28.6 ± 7.6
BMI, kg/m²		
	< 18.5	1,415 (4)
	18.5–24.9	29,533 (76)
	25.0–29.9	6,671 (17)
	30.0+	1,387 (4)
Neighborhood income[b], mean ±SD		11.2 ±3.0

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:

Francoise Clavel-Chapelon for the E3N Study Group. Cohort Profile: The French E3N Cohort Study. International Journal of Epidemiology 2015; 44: 801–809.

Cohort profile: **KORA**

Cooperative Health Research in the Region of Augsburg

Two cross-sectional population-representative surveys were conducted in 1994-1995 (S3 survey) and 1999-2001 (survey S4) in the city of Augsburg and two adjacent rural counties including inhabitants of German nationality aged 25 to 74.

Variable		Total	KORA, subcohorts	
			S3	S4
Baseline year, range		1994–2001	1994–1995	1999–2001
Enrolled, N		8,823	4,566	4,257
Included in mortality analyses, N		7,657	3,910	3,747
Included in stroke incidence analyses, N		4,195	2,182	2,013
Included in lung cancer incidence analyses, N		-	-	-
Age at baseline, mean ±SD[a]		49.4±13.9	49.4±13.9	49.3±13.8
Women, N (%)		2,481 (51)	1,308 (51)	1,173 (51)
Unemployed, N (%)		2,074 (43)	1,149 (45)	925 (41)
Marital status				
	Single	411 (8)	227 (9)	184 (8)
	Married	3,867 (80)	2,060 (80)	1,807 (79)
	Divorced	259 (5)	108 (4)	151 (7)
	Widowed	316 (7)	177 (7)	139 (6)
Smoking status, N (%)				
	Current	1,042 (21)	519 (20)	523 (23)
	Previous	1,460 (30)	740 (29)	720 (32)
	Never	2,351 (48)	1,313 (51)	1,038 (46)
Smoking intensity, g/d mean ±SD		16.1± 9.5	16.5 ± 9.5	15.7 ± 9.5
Smoking duration, yrs mean ±SD		24.7±11.8	25.2 ± 12.1	24.3 ± 11.6
BMI, kg/m²				
	< 18.5	21 (0)	13 (1)	8 (0)
	18.5–24.9	1,547 (32)	837 (33)	710 (31)
	25.0–29.9	2,112 (44)	1,116 (43)	996 (44)
	30.0+	1,173 (24)	606 (24)	567 (25)
Neighborhood income[b], mean ±SD		37.4 ±6.0	36.7±4.4	38.0±7.3

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:

Holle R, Happich M, Lowel H, Wichmann HE. KORA--a research platform for population based health research. Gesundheitswesen 2005; 67 Suppl 1: S19-S25.

Cohort profile: **VHM&PP**

Vorarlberg Health Monitoring and Prevention Programme

The VHM&PP is a population-based cohort recruited among all adults of the province of Vorarlberg, Austria. Vorarlberg is the western-most province of Austria consisting of towns and villages (30,000 inhabitatants and smaller) and significant altitude differences.

Variable		Total
Baseline year, range		1985–2005
Enrolled, N		170,250
Included in mortality analyses, N		144,383
Included in stroke incidence analyses, N		-
Included in lung cancer incidence analyses, N		140,272
Age at baseline, mean ±SD[a]		42.1±15.0
Women, N (%)		81117 (56)
Unemployed, N (%)		43,640 (30)
Marital status		
	Single	24,906 (17)
	Married	99,496 (69)
	Divorced	9,773 (7)
	Widowed	10,208 (7)
Smoking status, N (%)		
	Current	28916 (20)
	Previous	9004 (6)
	Never	106463 (74)
Smoking intensity, g/d mean ±SD		15.6 ±8.9
Smoking duration, yrs mean ±SD		13.4 ±8.3
BMI, kg/m^2		
	< 18.5	4457 (3)
	18.5–24.9	78677 (54)
	25.0–29.9	45591 (32)
	30.0+	15658 (11)
Municipality level income[b]**, mean ±SD**		22.9 ±1.7

[a]All characteristics shown for mortality analyses, similar for other endpoints
[b]EUR per 1,000, year 2001

Main reference:

Ulmer H, Kelleher CC, Fitz-Simon N et al. Secular trends in cardiovascular risk factors: an age-period cohort analysis of 698,954 health examinations in 181,350 Austrian men and women. Journal of Internal Medicine, 2007; 261: 566–576.

Section 2 Missing covariate value assessment

Multiple imputation (MI) is an attractive and effective approach for statistical analysis of incomplete data. The main idea is to create multiple data sets that reflect the potential values of the missing data. More precisely, random draws are made from the posterior distribution of the missing values given the observed data, usually under the missing at random (MAR) assumption. Estimates are combined across imputed data sets using Rubin's rules (Rubin, 1987). Although MI techniques have been proposed for imputing a covariate that may be complete missing from one study from the rest of the studies that are pooled under a multi-cohort approach, we decided against this considering the differences in the underlying populations between participating cohorts and instead prompted for the extensive sensitivity analysis on the choice of covariates in Model 3. We nevertheless tested robustness of the effect estimates for the association with total mortality to the missing data in the covariates that were available across cohorts and included in the main Model 3. When missing values occur in multiple variables, and in particular when these are a mixture of continuous and discrete variables, the method of multiple imputation by chained equations (MICE) is particularly attractive (van Buuren et al., 1999). This involves specifying a separate imputation model for each incomplete variable given all the other variables and repeatedly imputing the variables in an iterated sequence. As with MI in general, it is crucial that the imputation model is consistent (or congenial) with the model of interest, which will subsequently be fitted to the imputed data sets. Hence, MICE was applied for each cohort with availability of covariate data but with missing values to produce 5 complete datasets per cohort. In this way the imputation of the missing values was based on the cohort-specific data and did not use information from the rest contributing cohorts in the pooled data set. Consequently, the cohort-specific corresponding complete datasets were pooled and Model 3 was applied for each of the 5 complete pooled datasets. The effect estimates from these models were pooled using the Rubin's rules. We applied MICE by filling in missing data for all covariates in main Model 3. We used the R library *mice*.

References:

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons, Inc.; 1987.

van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Statistics in medicine 1999;18:681-694.

Section 3 Statistical software

ELAPSE pooled datasets were stored in Yoda secure data management service of Utrecht University. For statistical analyses, we used an R-Studio Server Pro environment running on a dedicated physical server of Utrecht University (16-core CPU, 192 GB RAM). All the analyses and output generation were done in this environment. Using a secure remote access environment prevented database distribution and assured that the latest database version was used for analyses. Analyses were performed in R, version 3.4.0 (R Core Team). The following packages were used in the analyses:

coxme (2.2-10)	Matrix (1.2-14)
data.table (1.12.8)	mice (2.46.0)
dplyr (0.8.4)	Multcomp (1.4-8)
foreach (1.4.4)	Rms (5.1-2)
ggplot2 (3.3.3)	Splines (3.4.0)
glmnet (2.0-16)	survey (3.33-2)
Hmisc (4.1-1)	survival (2.42-3)
MASS (7.3-50)	VIM (4.7.0)

References:

R Core Team. R: A language and environment for statistical computing. 2020.https://www.r-project.org.

Yoda. Yoda – a research data management service. 2020. https://www.uu.nl/en/research/yoda.

Section 4 Exposure distribution

Table S3 Distribution of air pollution exposure at participant addresses in pooled cohort

Pollutant	Mean	SD	IQR	Min	P5	P25	P50	P75	P95	Max
POOLED COHORT										
PM2.5	15.02	3.22	4.48	3.24	8.63	12.84	15.50	17.32	19.43	27.49
NO_2	25.00	8.05	10.15	2.68	12.91	19.52	24.14	29.68	39.53	81.02
BC	1.52	0.42	0.50	0.11	0.74	1.29	1.56	1.79	2.13	4.62
O_3	85.32	8.93	14.12	36.32	70.51	78.54	86.32	92.67	97.34	115.51
CEANS-SDPP										
PM2.5	7.63	0.92	0.75	3.79	5.91	7.36	7.77	8.11	8.67	10.96
NO_2	15.45	4.29	5.38	2.96	7.81	12.78	15.56	18.16	22.46	37.09
BC	0.56	0.19	0.30	0.14	0.30	0.41	0.52	0.71	0.92	1.39
O_3	77.56	1.92	2.59	68.37	74.41	76.37	77.49	78.95	80.62	85.01
CEANS-SIXTY										
PM2.5	8.31	0.91	0.88	3.24	6.83	7.95	8.42	8.83	9.45	11.01
NO_2	20.68	6.13	7.00	2.68	10.70	17.03	20.54	24.03	31.28	47.88
BC	0.80	0.25	0.32	0.11	0.39	0.64	0.81	0.96	1.17	2.10
O_3	76.70	2.51	2.88	63.15	72.58	75.38	76.83	78.26	80.72	83.79
CEANS-SALT										
PM2.5	8.38	0.84	0.88	3.47	7.13	7.99	8.48	8.87	9.52	11.37
NO_2	21.29	6.18	7.33	2.98	11.21	17.55	21.02	24.88	31.87	50.32
BC	0.83	0.25	0.31	0.16	0.41	0.67	0.83	0.99	1.19	2.43
O_3	76.57	2.72	2.88	57.17	72.11	75.26	76.78	78.14	80.77	84.87
CEANS-SNACK										
PM2.5	8.56	0.84	0.59	5.16	7.17	8.36	8.61	8.96	9.58	11.37
NO_2	27.39	5.09	7.38	11.62	18.27	23.56	28.50	30.95	33.94	42.61
BC	1.08	0.15	0.15	0.43	0.92	0.98	1.05	1.13	1.34	1.74
O_3	75.10	2.67	2.91	58.63	70.18	73.97	75.46	76.88	78.18	82.50
DCH										
PM2.5	13.20	1.43	1.58	7.29	11.31	12.31	12.91	13.89	15.93	19.49
NO_2	28.04	6.84	10.00	6.40	16.54	23.26	28.32	33.26	38.22	72.23
BC	1.34	0.35	0.48	0.35	0.73	1.11	1.35	1.59	1.88	3.66
O_3	77.52	5.11	7.18	50.96	67.53	74.34	79.09	81.52	83.59	87.79

Table S3 continued.

DNC-1993										
PM2.5	12.74	1.54	1.87	6.48	10.37	11.72	12.65	13.58	15.60	19.14
NO_2	21.90	8.00	10.52	4.54	10.18	16.35	20.37	26.87	37.07	72.23
BC	1.09	0.37	0.52	0.13	0.59	0.80	1.03	1.32	1.79	3.66
O_3	80.41	4.01	3.97	50.96	72.53	78.89	81.20	82.85	85.23	91.87
DNC-1999										
PM2.5	13.80	1.51	2.34	6.89	11.35	12.75	13.60	15.09	16.31	19.49
NO_2	25.85	8.47	13.82	6.42	13.71	19.42	23.76	33.24	38.95	54.26
BC	1.30	0.38	0.55	0.36	0.72	1.02	1.26	1.58	1.90	2.74
O_3	80.61	3.85	3.89	57.02	73.31	79.09	81.35	82.97	85.27	91.83
EPIC-NL-MORGEN										
PM2.5	17.95	1.01	1.42	11.99	16.11	17.30	17.92	18.72	19.42	21.70
NO_2	34.55	6.05	8.97	11.00	26.18	29.97	33.60	38.94	44.80	68.66
BC	1.72	0.28	0.44	0.97	1.36	1.48	1.69	1.92	2.20	3.39
O_3	73.45	7.72	9.91	36.32	57.63	68.57	76.75	78.48	81.86	84.48
EPIC-NL-PROSPECT										
PM2.5	16.87	0.77	0.96	12.47	15.65	16.39	16.94	17.35	18.02	19.86
NO_2	35.96	5.41	7.27	19.58	27.40	32.52	35.46	39.79	44.63	62.15
BC	1.66	0.27	0.38	1.06	1.28	1.46	1.61	1.84	2.13	2.91
O_3	72.66	2.72	3.29	54.53	67.74	71.24	73.06	74.53	76.35	79.47
HNR										
PM2.5	19.58	0.86	1.05	14.83	18.06	19.08	19.77	20.13	20.76	22.96
NO_2	37.78	4.66	5.03	25.23	31.26	34.87	37.54	39.90	45.83	75.07
BC	1.99	0.25	0.29	1.28	1.60	1.83	1.97	2.12	2.40	3.85
O_3	78.96	2.79	2.99	53.14	73.79	77.80	79.35	80.78	82.42	84.24
E3N										
PM2.5	17.02	2.92	3.52	5.29	12.91	15.10	16.47	18.62	22.90	27.49
NO_2	26.36	9.75	12.54	3.46	13.40	19.32	24.57	31.86	45.59	81.02
BC	1.79	0.48	0.65	0.88	1.20	1.42	1.69	2.07	2.73	4.62
O_3	87.71	7.99	8.75	56.52	76.08	82.56	87.01	91.32	103.88	115.51
KORA-S3										
PM2.5	16.30	0.88	0.96	13.26	14.51	15.89	16.37	16.85	17.62	18.68
NO_2	21.13	3.30	4.32	10.42	16.30	18.88	20.97	23.21	26.41	41.72
BC	1.55	0.16	0.16	1.27	1.36	1.44	1.52	1.61	1.85	2.80
O_3	85.94	1.48	1.66	74.73	83.31	85.23	86.12	86.89	87.92	89.24

Table S3 continued.

KORA-S4									
PM2.5	16.20	0.90	1.01	11.78	14.40	15.75	16.35	16.76	17.54	18.55
NO_2	21.05	3.39	4.49	9.68	15.91	18.76	20.82	23.24	26.50	41.72
BC	1.55	0.17	0.17	1.26	1.34	1.44	1.51	1.61	1.87	2.77
O_3	86.04	1.52	1.79	74.79	83.44	85.32	86.24	87.10	88.06	89.37
VHM&PP										
PM2.5	15.73	2.64	3.60	4.56	10.86	13.94	16.51	17.54	19.16	20.91
NO_2	21.96	5.34	6.99	3.85	12.29	18.63	22.46	25.62	29.70	48.28
BC	1.64	0.26	0.35	0.87	1.21	1.46	1.65	1.81	2.03	3.02
O_3	92.61	3.63	5.64	74.03	86.90	89.87	92.80	95.51	97.97	104.01

SD is standard deviation, IQR is interquartile range, P5 to P95 are percentiles.Units for pollutants: $PM_{2.5}$– µg/m^3, NO_2 – µg/m^3, BC – 10-5/m, O_3 – µg/m^3.

Table S4 Spearman correlations between air pollutants at participant addresses

Pollutant	PM2.5	BC	O_3
CEANS-SDPP			
NO_2	0.60	0.64	-0.68
PM2.5		0.58	-0.14
BC			-0.27
CEANS-SIXTY			
NO_2	0.63	0.81	-0.67
PM2.5		0.53	-0.42
BC			-0.66
CEANS-SALT			
NO_2	0.63	0.81	-0.69
PM2.5		0.52	-0.46
BC			-0.69
CEANS-SNACK			
NO_2	0.76	0.37	-0.72
PM2.5		0.26	-0.62
BC			-0.59
DCH			
NO_2	0.74	0.91	-0.59
PM2.5		0.70	-0.52
BC			-0.58
DNC-1993			
NO_2	0.58	0.90	-0.35
PM2.5		0.69	-0.27
BC			-0.38
DNC-1999			
NO_2	0.57	0.93	-0.16
PM2.5		0.63	-0.10
BC			-0.16
EPIC-NL-MORGEN			
NO_2	0.20	0.82	-0.77
PM2.5		0.43	0.18
BC			-0.50
EPIC-NL-PROSPECT			
NO_2	0.42	0.89	-0.85
PM2.5		0.40	-0.43
BC			-0.81

Table S4 continued.

HNR			
NO_2	0.64	0.83	-0.76
PM2.5		0.60	-0.73
BC			-0.73
E3N			
NO_2	0.77	0.90	-0.51
PM2.5		0.68	-0.44
BC			-0.37
KORA-S3			
NO_2	0.50	0.75	-0.69
PM2.5		0.50	-0.39
BC			-0.68
KORA-S4			
NO_2	0.58	0.67	-0.67
PM2.5		0.59	-0.38
BC			-0.61
VHM&PP			
NO_2	0.62	0.90	-0.82
PM2.5		0.74	-0.71
BC			-0.87
POPULATION-WEIGHTED MEAN OF WITHIN-COHORT CORRELATIONS			
NO_2	0.62	0.88	-0.69
PM2.5		0.67	-0.52
BC			-0.67

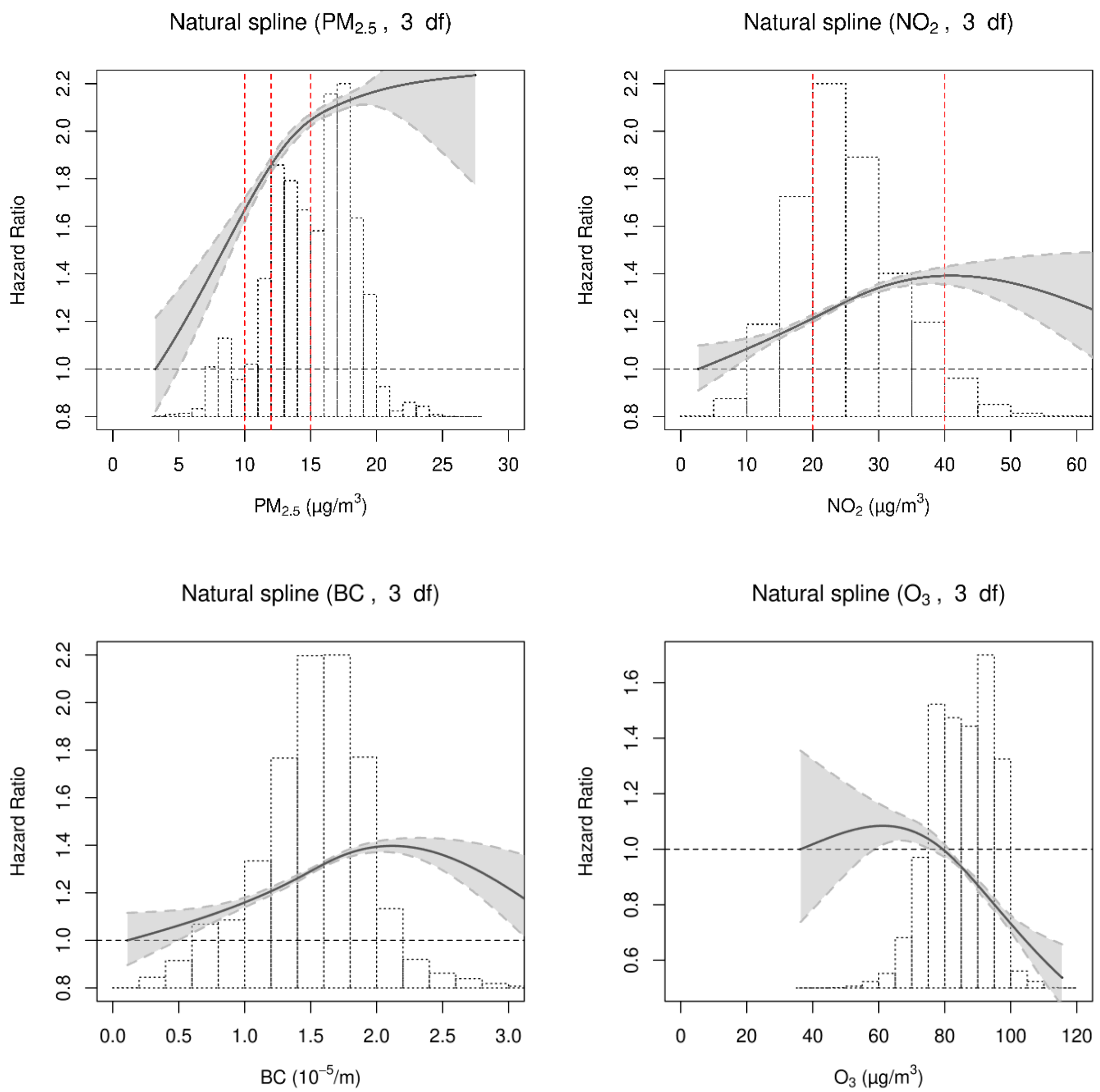
Table S5 Hazard ratios of associations between mortality and air pollution exposure **represented by quartiles** of the pooled cohort distribution

Pollutant	Quartile[1]	Follow-up time	Natural-cause mortality		Cardiovascular mortality		Respiratory mortality	
			Deaths (No.)	HR (95% CI)	Deaths (No.)	HR (95% CI)	Deaths (No.)	HR (95% CI)
NO_2	1st	20.1	10267	NA	3627	NA	605	NA
	2nd	20.5	11770	1.081 (1.052, 1.110)	4252	1.070 (1.023, 1.120)	681	1.096 (0.980, 1.227)
	3rd	20.2	12965	1.132 (1.102, 1.164)	4644	1.128 (1.077, 1.181)	706	1.090 (0.971, 1.222)
	4th	17.1	12129	1.186 (1.149, 1.224)	3019	1.186 (1.118, 1.257)	873	1.246 (1.100, 1.412)
PM2.5	1st	18.1	12744	NA	3757	NA	873	NA
	2nd	19.8	12771	1.107 (1.078, 1.137)	3913	1.126 (1.071, 1.183)	907	1.196 (1.082, 1.322)
	3rd	20.2	10851	1.131 (1.097, 1.167)	3734	1.125 (1.066, 1.188)	607	1.105 (0.975, 1.253)
	4th	19.9	10765	1.190 (1.151, 1.229)	4138	1.225 (1.159, 1.294)	478	1.029 (0.892, 1.186)
BC	1st	17.5	11853	NA	3245	NA	841	NA
	2nd	19.9	11742	1.126 (1.093, 1.160)	3905	1.167 (1.104, 1.234)	732	1.135 (1.014, 1.271)
	3rd	20.8	11893	1.156 (1.121, 1.192)	4256	1.202 (1.136, 1.273)	698	1.186 (1.054, 1.333)
	4th	19.7	11643	1.194 (1.157, 1.233)	4136	1.213 (1.143, 1.287)	594	1.142 (1.004, 1.299)
O_3	1st	16.2	12712	NA	3092	NA	979	NA
	2nd	17.4	11347	0.933 (0.905, 0.961)	2710	0.931 (0.874, 0.993)	764	0.866 (0.777, 0.965)
	3rd	21.8	12049	0.904 (0.856, 0.953)	5032	0.899 (0.814, 0.994)	513	0.873 (0.686, 1.111)
	4th	22.5	11023	0.810 (0.766, 0.856)	4708	0.807 (0.729, 0.893)	609	1.002 (0.781, 1.284)

[1] First quartile is the reference

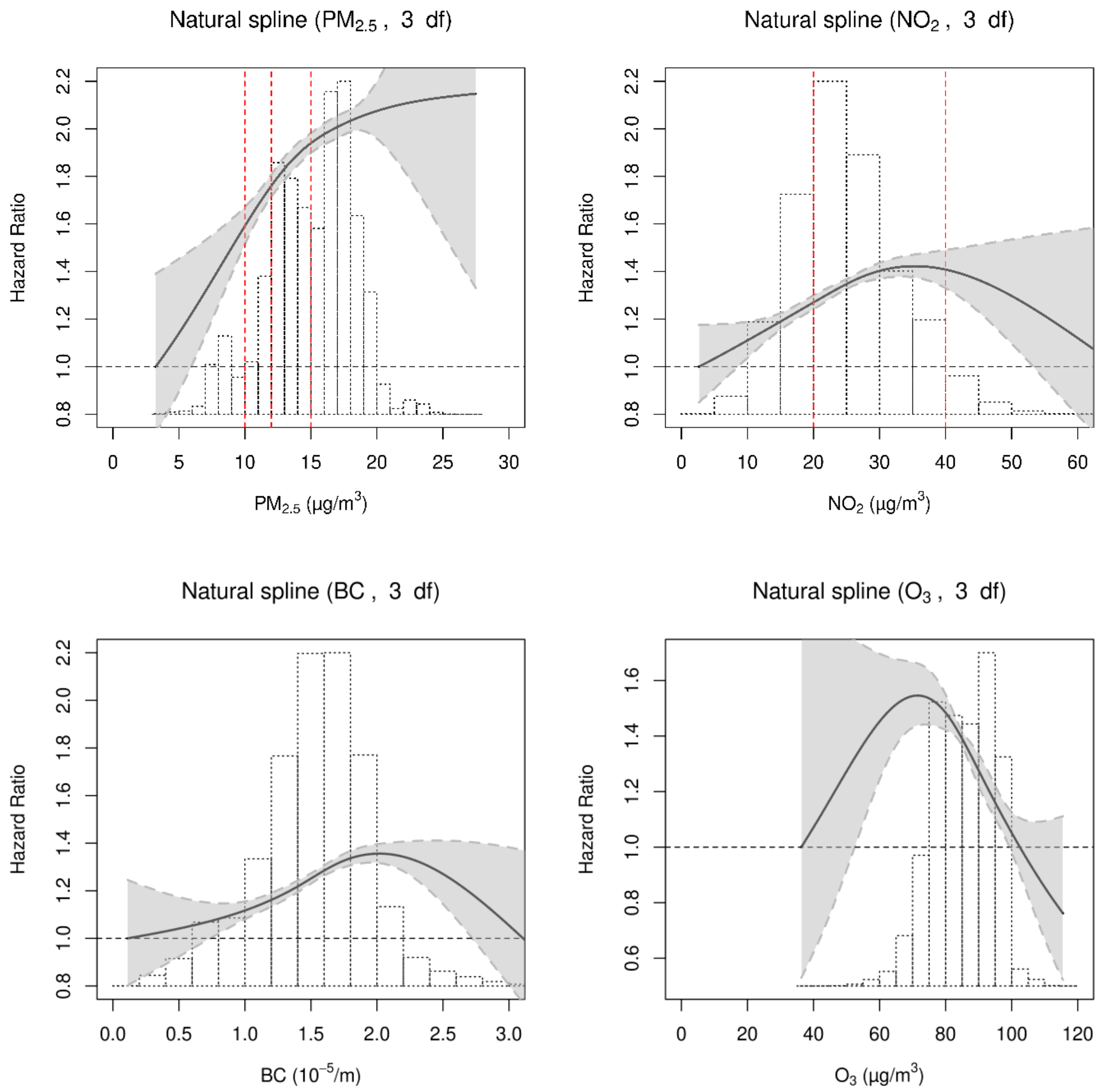
Section 5 Concentration-response functions

Figure S1 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **natural mortality**



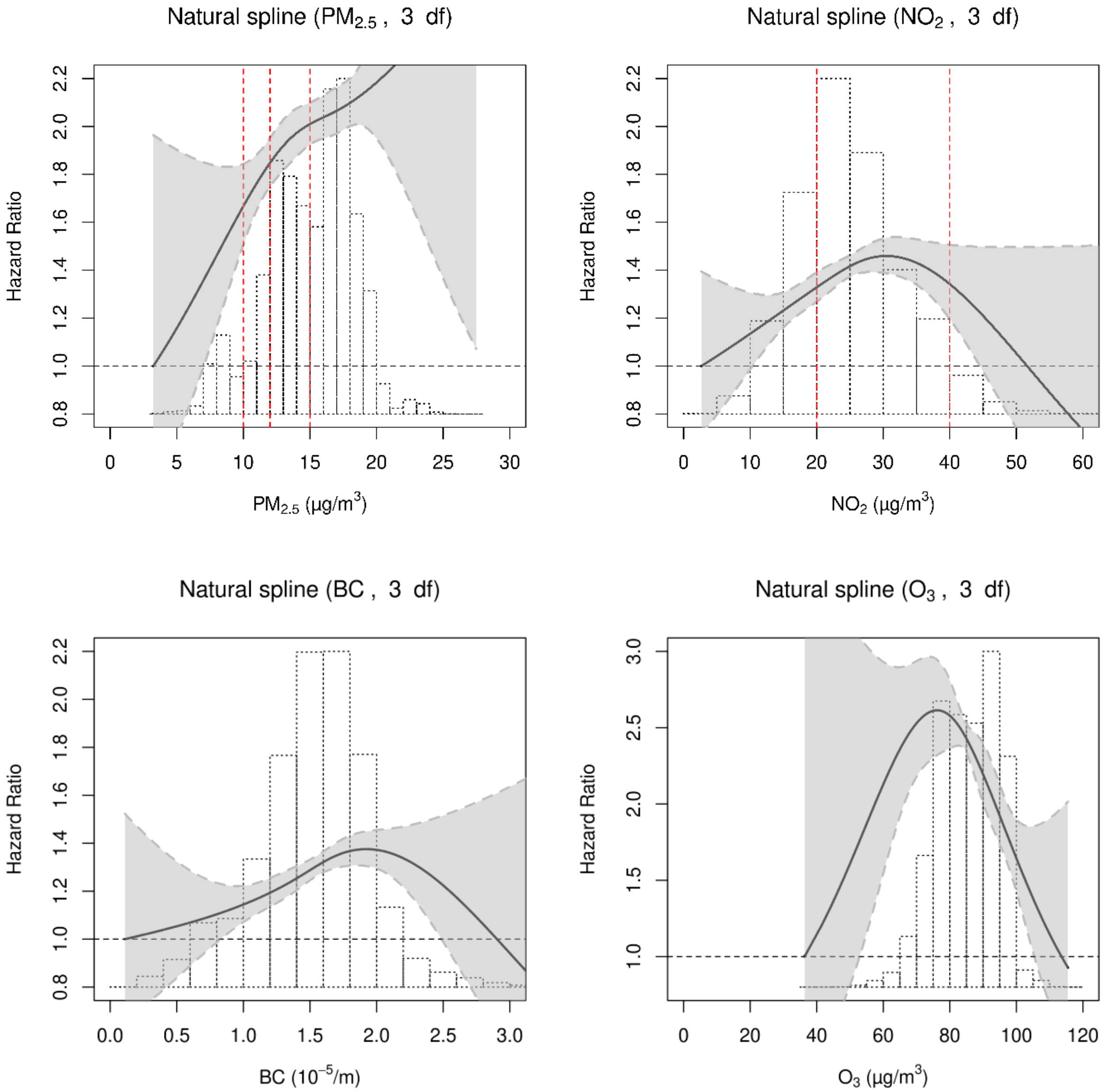
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m³ for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S2 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **cardiovascular disease mortality**



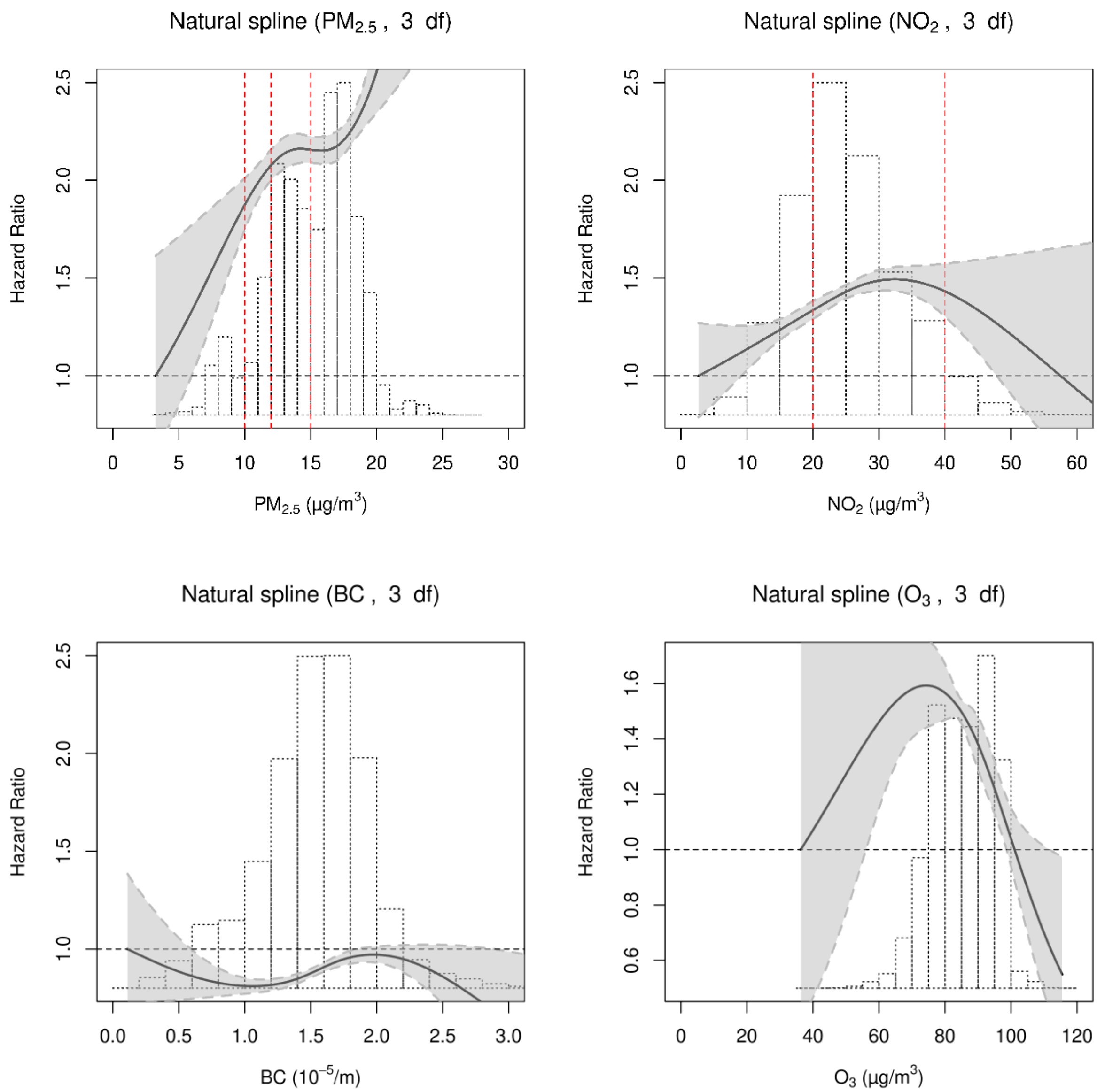
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S3 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **cerebrovascular disease mortality**



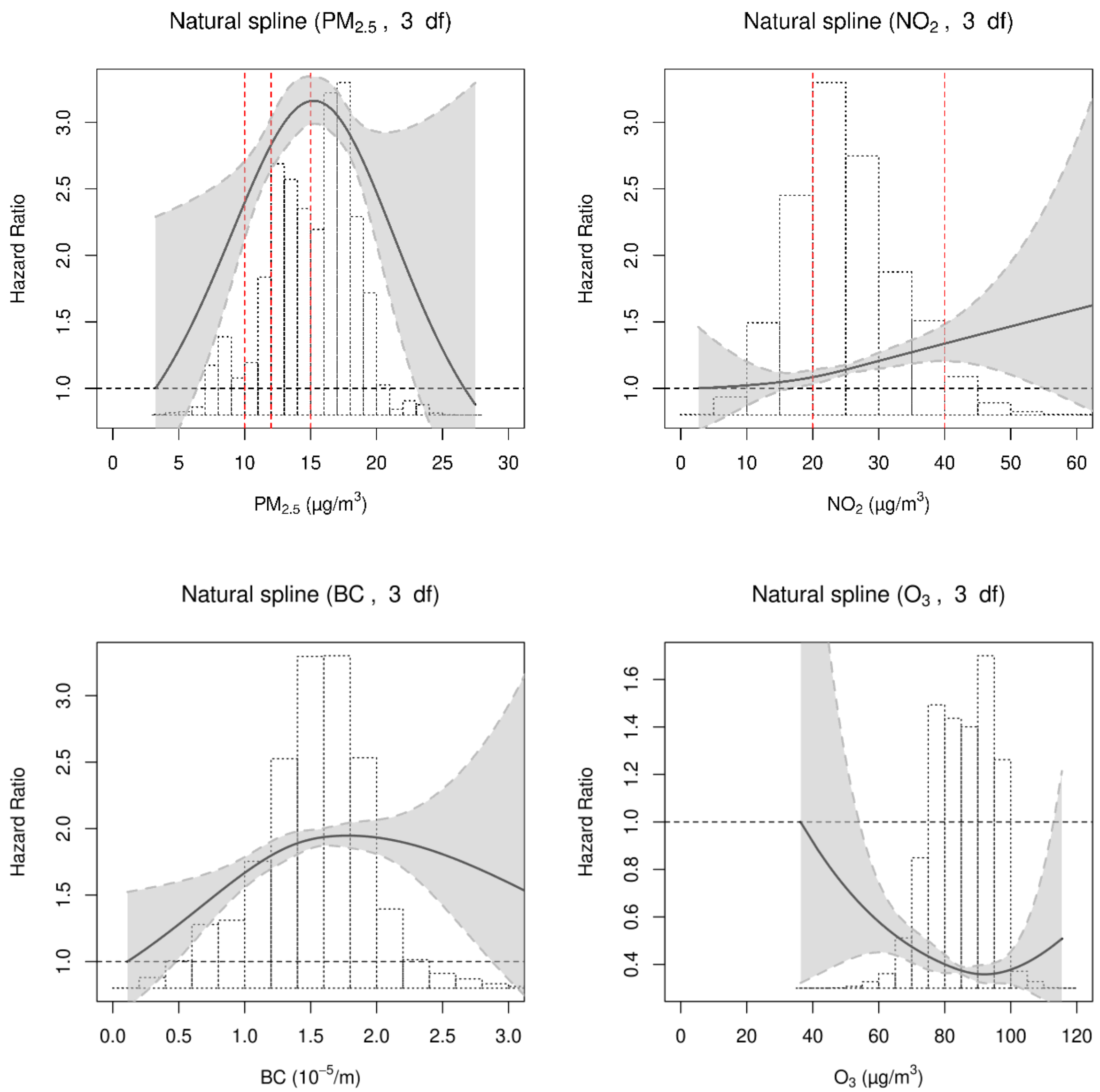
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S4 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **ischemic heart disease mortality**



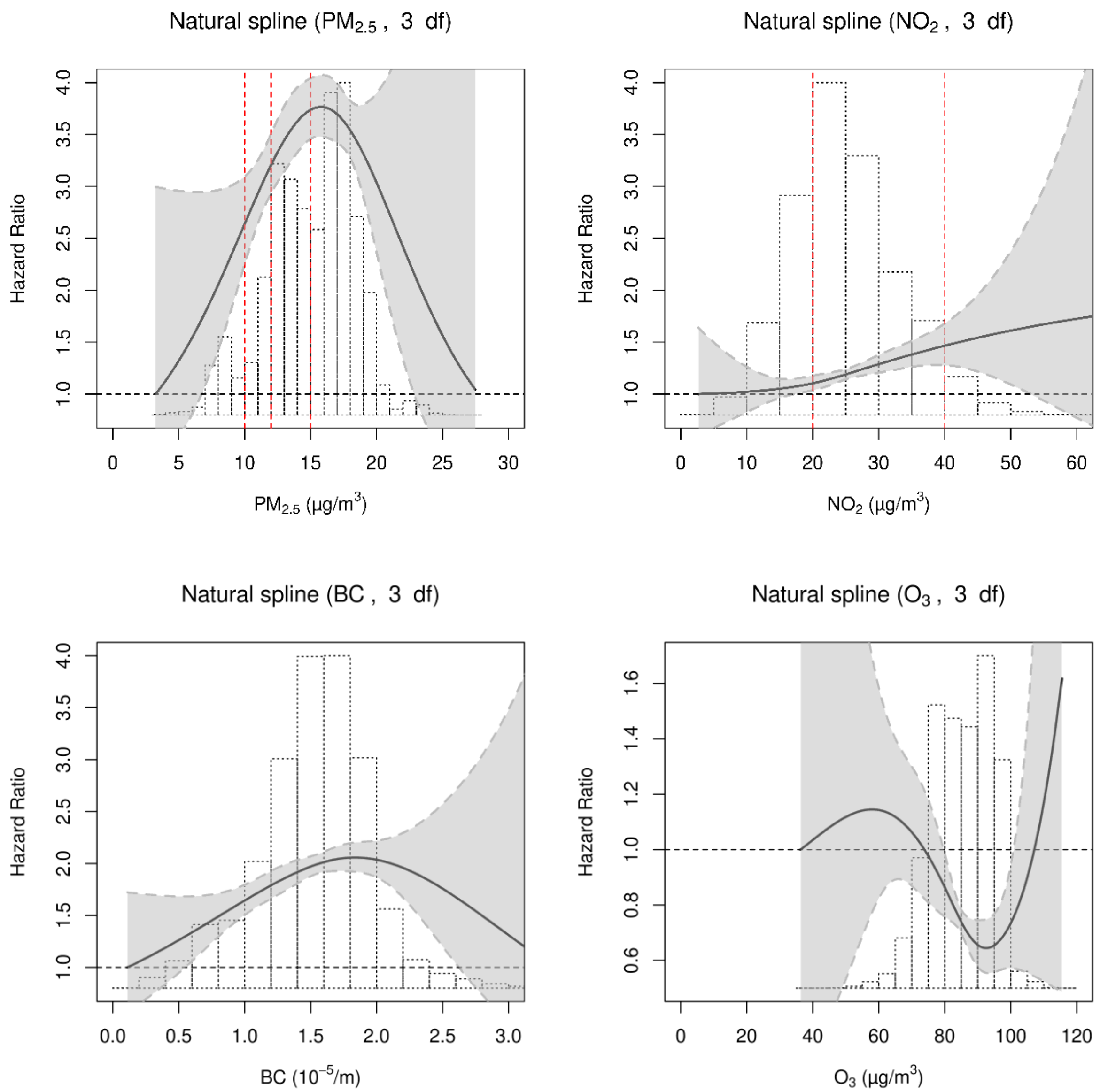
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m³ for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S5 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **respiratory mortality**



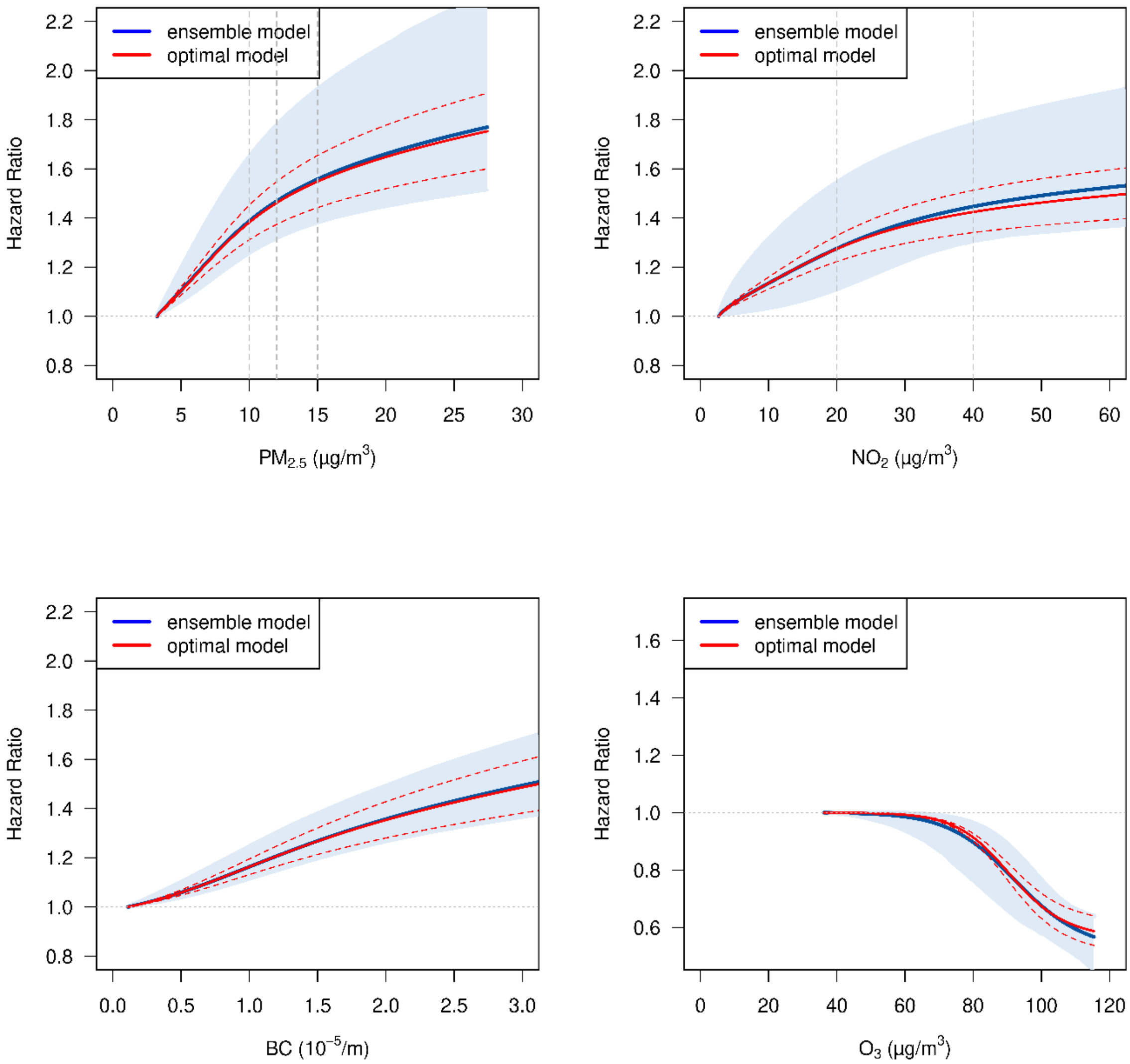
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m[3] for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S6 Natural cubic splines (3 degrees of freedom) for associations between air pollution exposure and **chronic obstructive pulmonary disease mortality**



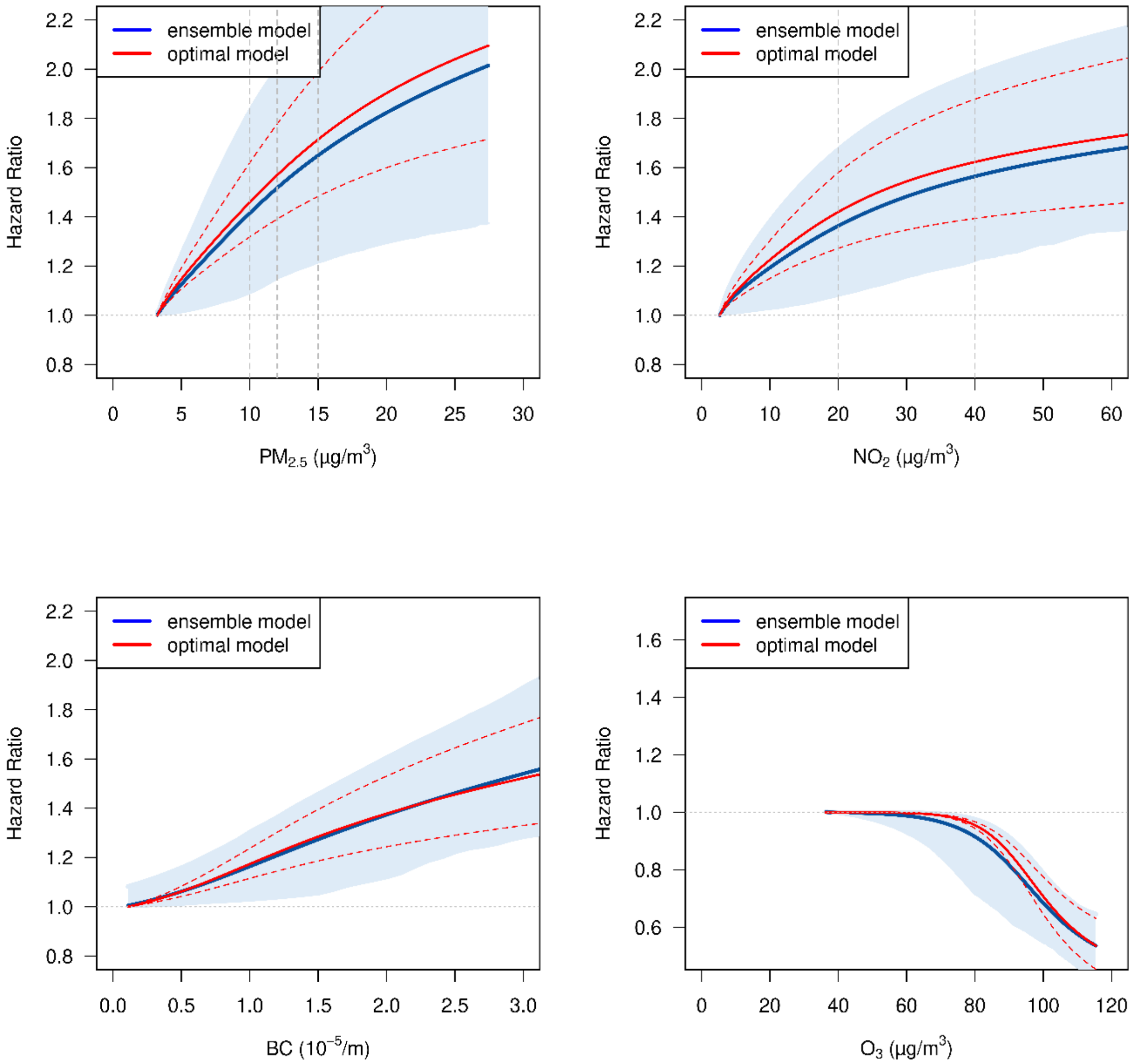
Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S7 Shape-Constrained Health Impact Function for associations between air pollution exposure and **natural mortality**



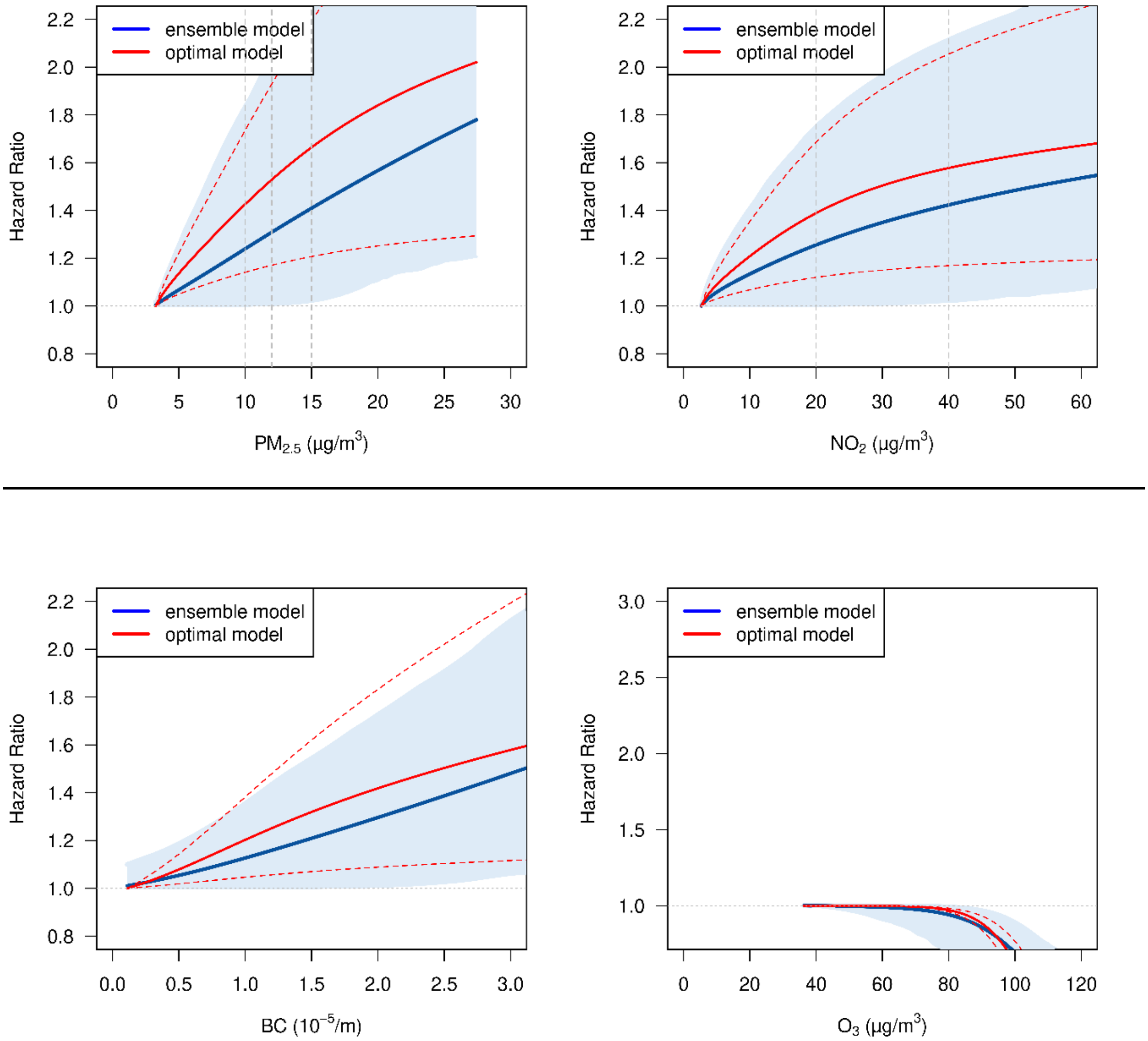
X-axis truncated at 30, 60, 3 and 120 μg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S8 Shape-Constrained Health Impact Function for associations between air pollution exposure and **cardiovascular disease mortality**



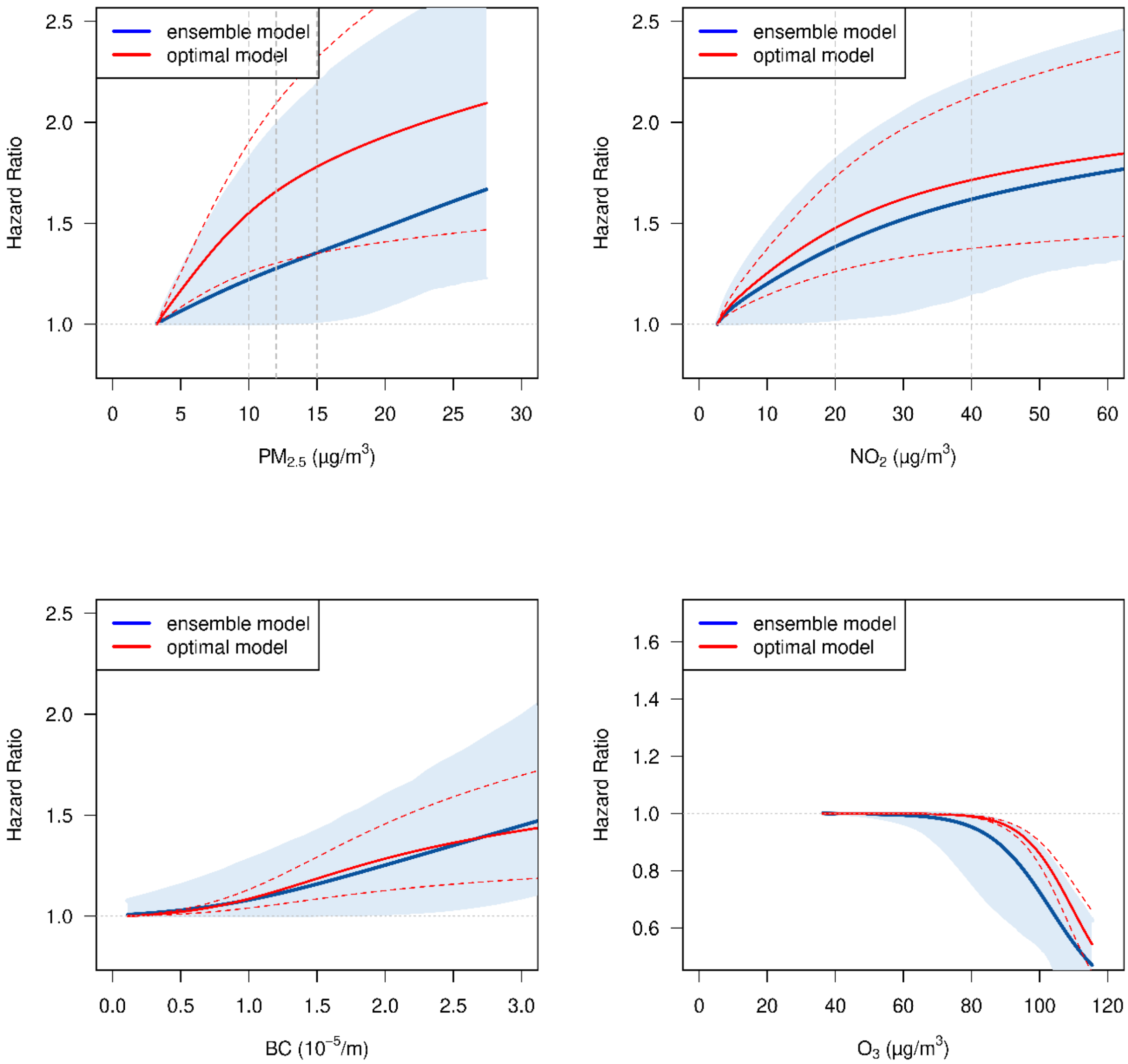
X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S9 Shape-Constrained Health Impact Function for associations between air pollution exposure and **cerebrovascular disease mortality**



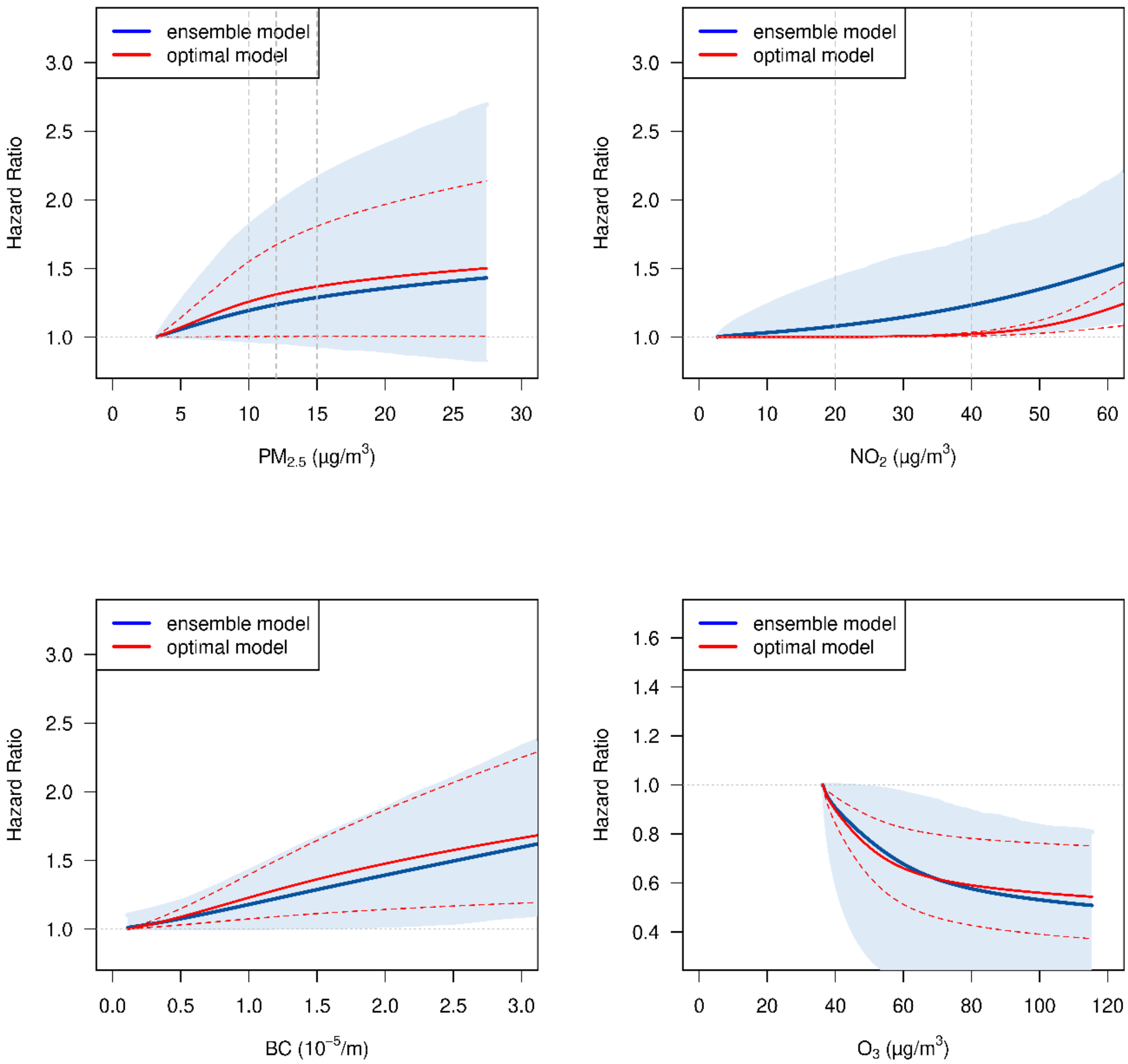
X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S10 Shape-Constrained Health Impact Function for associations between air pollution exposure and **ischemic heart disease mortality**



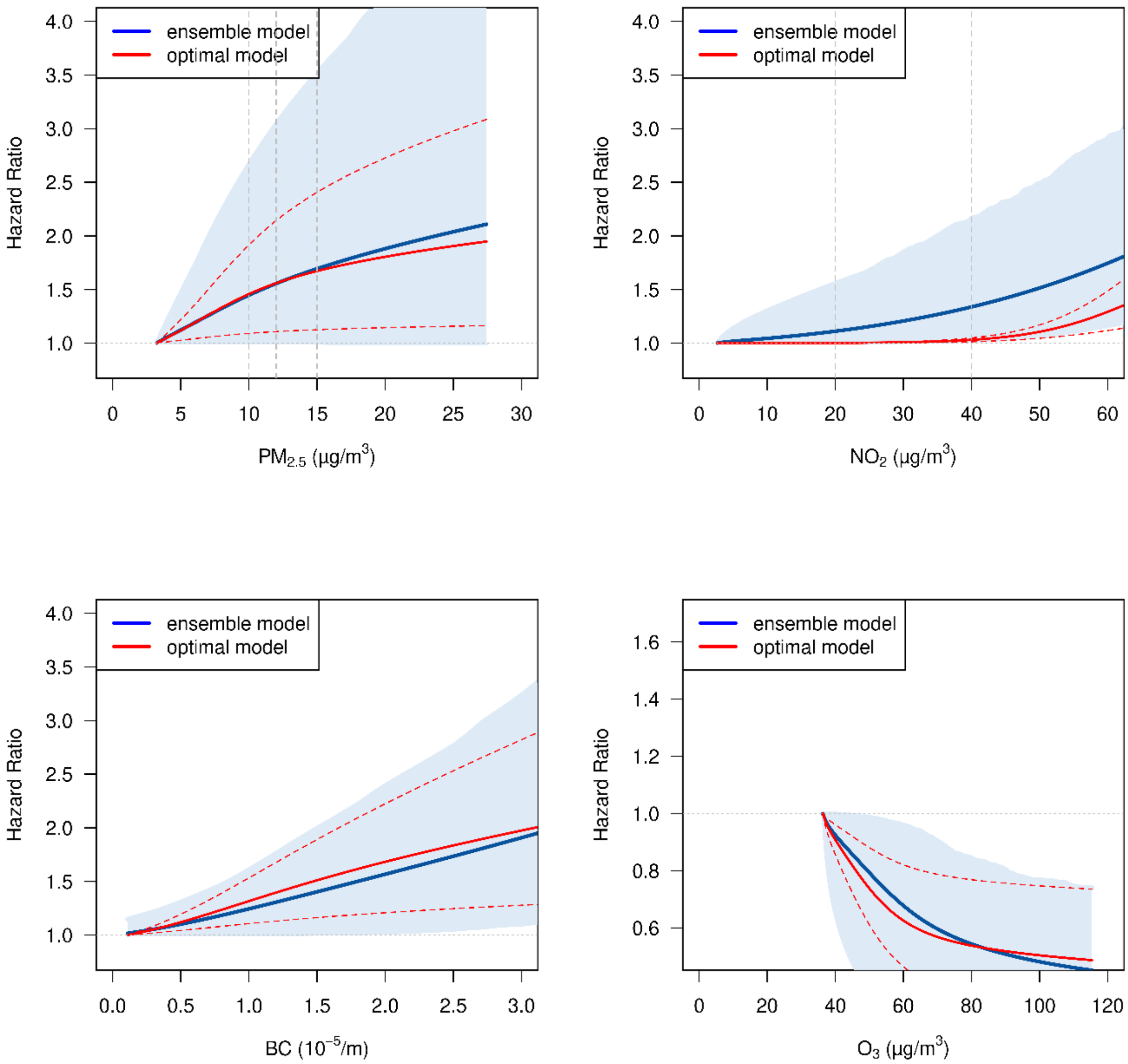
X-axis truncated at 30, 60, 3 and 120 μg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S11 Shape-Constrained Health Impact Function for associations between air pollution exposure and **respiratory mortality**



X-axis truncated at 30, 60, 3 and 120 µg/m³ for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Figure S12 Shape-Constrained Health Impact Function for associations between air pollution exposure and **chronic obstructive pulmonary disease mortality**



X-axis truncated at 30, 60, 3 and 120 µg/m³ for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Section 6 Two-pollutant analysis

Table S6 Hazard ratios for associations between air pollution and **natural mortality** in two-pollutant models

Pollutant	Single pollutant HR	HR adjusted for PM2.5	HR adjusted for NO2	HR adjusted for BC	HR adjusted for O_3
PM2.5	1.130 (1.106, 1.155)	NA	1.083 (1.054, 1.113)	1.092 (1.062, 1.123)	1.089 (1.061, 1.117)
NO_2	1.086 (1.070, 1.102)	1.050 (1.031, 1.070)	NA	1.074 (1.038, 1.112)	1.053 (1.032, 1.074)
BC	1.081 (1.065, 1.098)	1.039 (1.019, 1.060)	1.012 (0.977, 1.048)	NA	1.044 (1.024, 1.065)
O_3	0.896 (0.878, 0.914)	0.935 (0.913, 0.957)	0.940 (0.914, 0.966)	0.930 (0.906, 0.955)	NA

NA=not applicable; Two-pollutant models of BC and NO_2 are difficult to interpret because of high correlation between BC and NO_2.

N=325,367; HR (95% confidence interval) presented for the following increments: PM2.5 – 5 μg/m^3, NO_2 – 10 μg/m^3, BC – 0.5*10-5/m, O_3 – 10 μg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighborhood-level mean income.

Table S7 Hazard ratios for associations between air pollution and **cardiovascular mortality** in two-pollutant models

Pollutant	Single pollutant HR	HR adjusted for $PM_{2.5}$	HR adjusted for NO2	HR adjusted for BC	HR adjusted for O_3
$PM_{2.5}$	1.135 (1.095, 1.176)	NA	1.100 (1.053, 1.150)	1.112 (1.061, 1.165)	1.100 (1.054, 1.149)
NO_2	1.089 (1.060, 1.120)	1.043 (1.007, 1.079)	NA	1.077 (1.012, 1.146)	1.051 (1.010, 1.094)
BC	1.085 (1.055, 1.116)	1.026 (0.988, 1.066)	1.013 (0.950, 1.081)	NA	1.039 (0.997, 1.082)
O_3	0.887 (0.854, 0.922)	0.941 (0.898, 0.987)	0.933 (0.882, 0.987)	0.921 (0.871, 0.973)	NA

NA=not applicable; N=325,367; HR (95% confidence interval) presented for the following increments: $PM_{2.5}$– 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Table S8 Hazard ratios for associations between air pollution and **respiratory mortality** in two-pollutant models

Pollutant	Single pollutant HR	HR adjusted for $PM_{2.5}$	HR adjusted for NO_2	HR adjusted for BC	HR adjusted for O_3
$PM_{2.5}$	1.054 (0.961, 1.156)	NA	0.944 (0.842, 1.06)	0.962 (0.854, 1.082)	0.980 (0.880, 1.091)
NO_2	1.101 (1.038, 1.168)	1.125 (1.045, 1.212)	NA	1.143 (0.998, 1.309)	1.076 (0.993, 1.165)
BC	1.084 (1.02, 1.151)	1.101 (1.019, 1.19)	0.959 (0.835, 1.101)	NA	1.045 (0.967, 1.13)
O_3	0.890 (0.821, 0.966)	0.882 (0.802, 0.971)	0.952 (0.854, 1.063)	0.924 (0.832, 1.027)	NA

NA=not applicable; N=325,367; HR (95% confidence interval) presented for the following increments: $PM_{2.5}$ – 5 μg/m^3, NO_2 – 10 μg/m^3, BC – 0.5*10-5/m, O_3 – 10 μg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Section 7 Sensitivity analyses

Figure S13 Temporal trends in PM2.5, NO_2, BC and O_3 concentrations based upon the Danish DEHM model for different regions in Europe

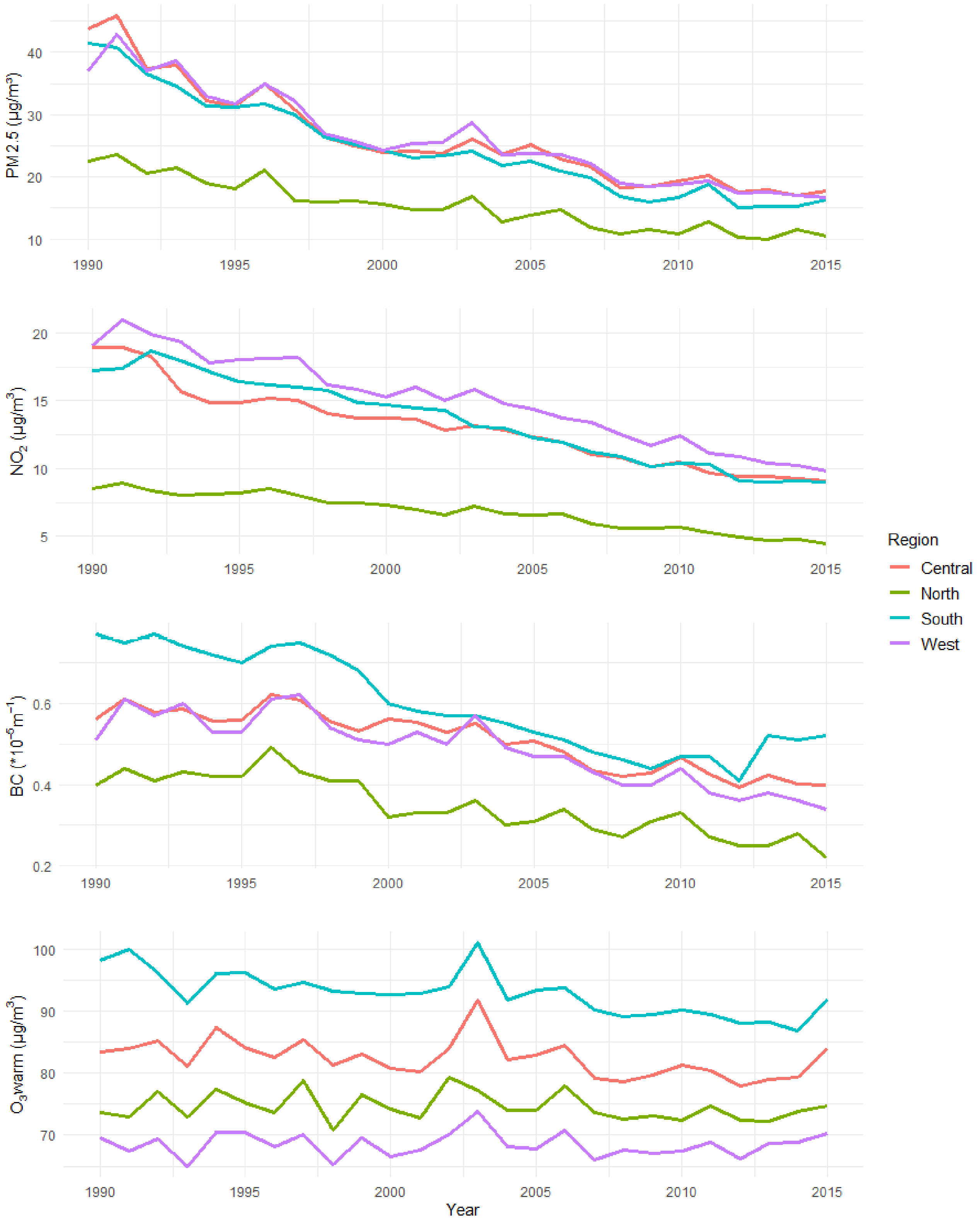
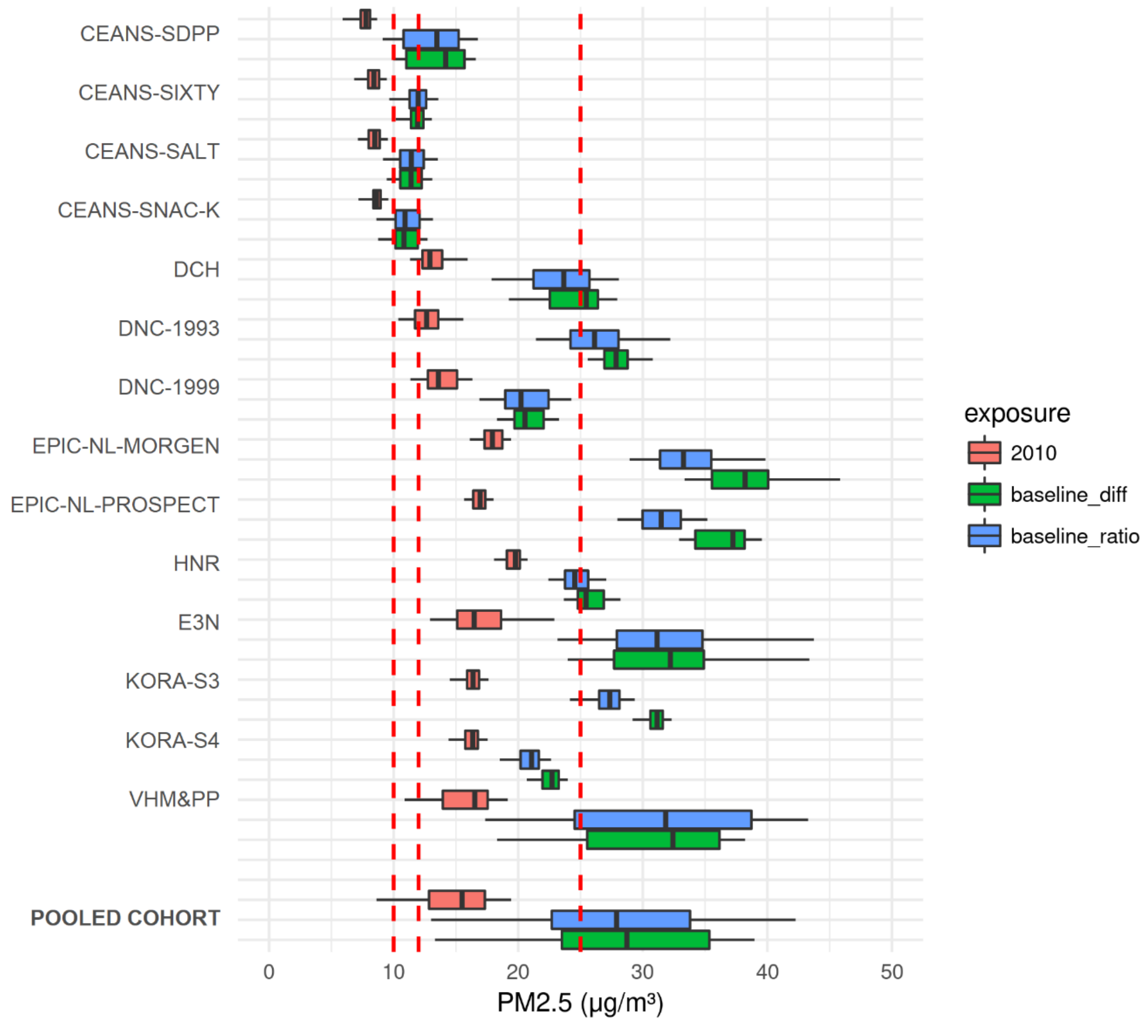


Figure S14 Distribution of PM2.5, NO_2, BC and O_3 exposure at participant addresses using 2010 and back-extrapolated exposure at baseline year



Red: 2010 exposure; green: backextapolated exposure using the difference method; blue: backextapolated exposure using the the ratio method.The boundary of the box closest to zero indicates P25; furthest from zero – P75; bold line in the middle of the box – P50; whiskers indicate P5 and P95.

Figure S14 continued.

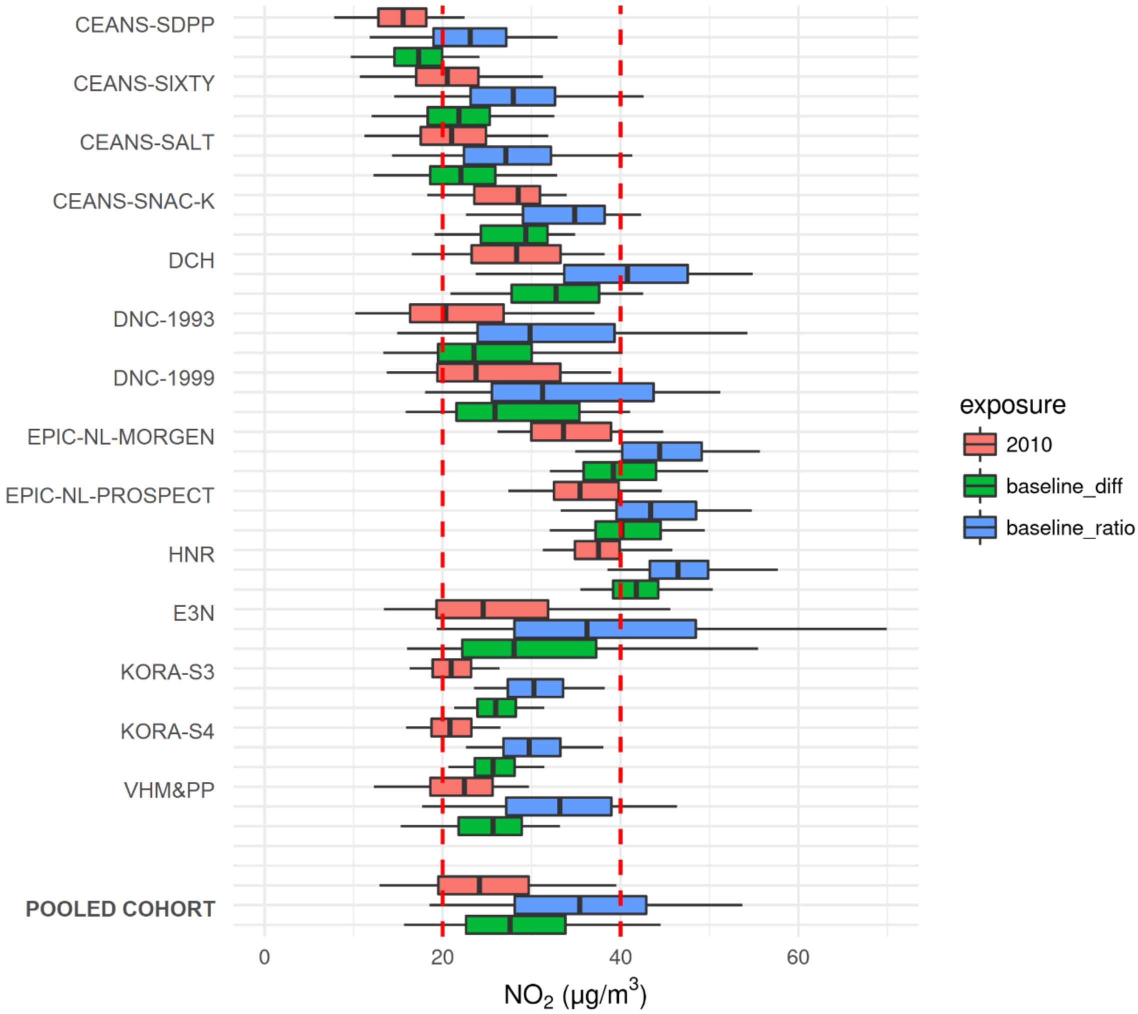


Figure S14 continued.

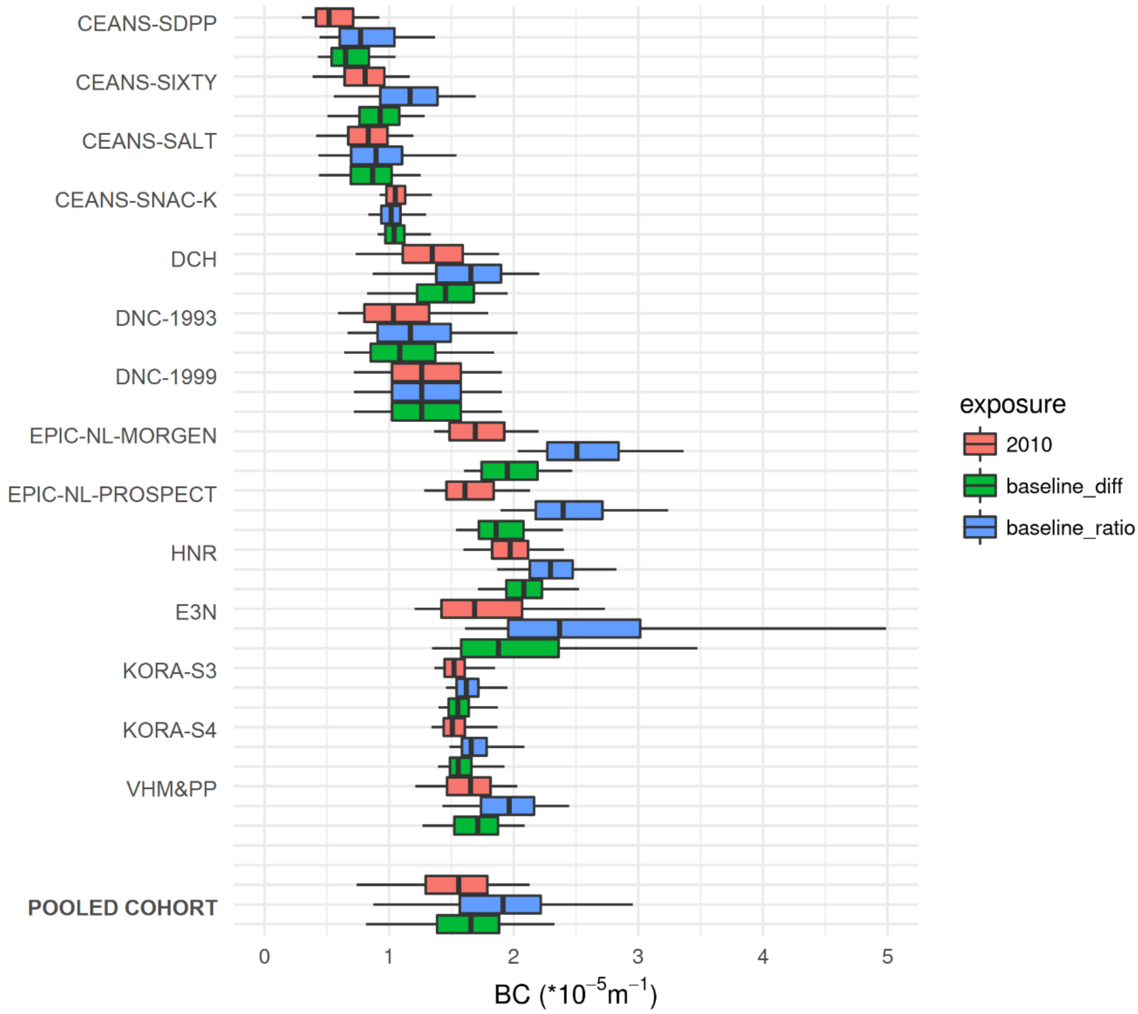


Figure S14 continued.

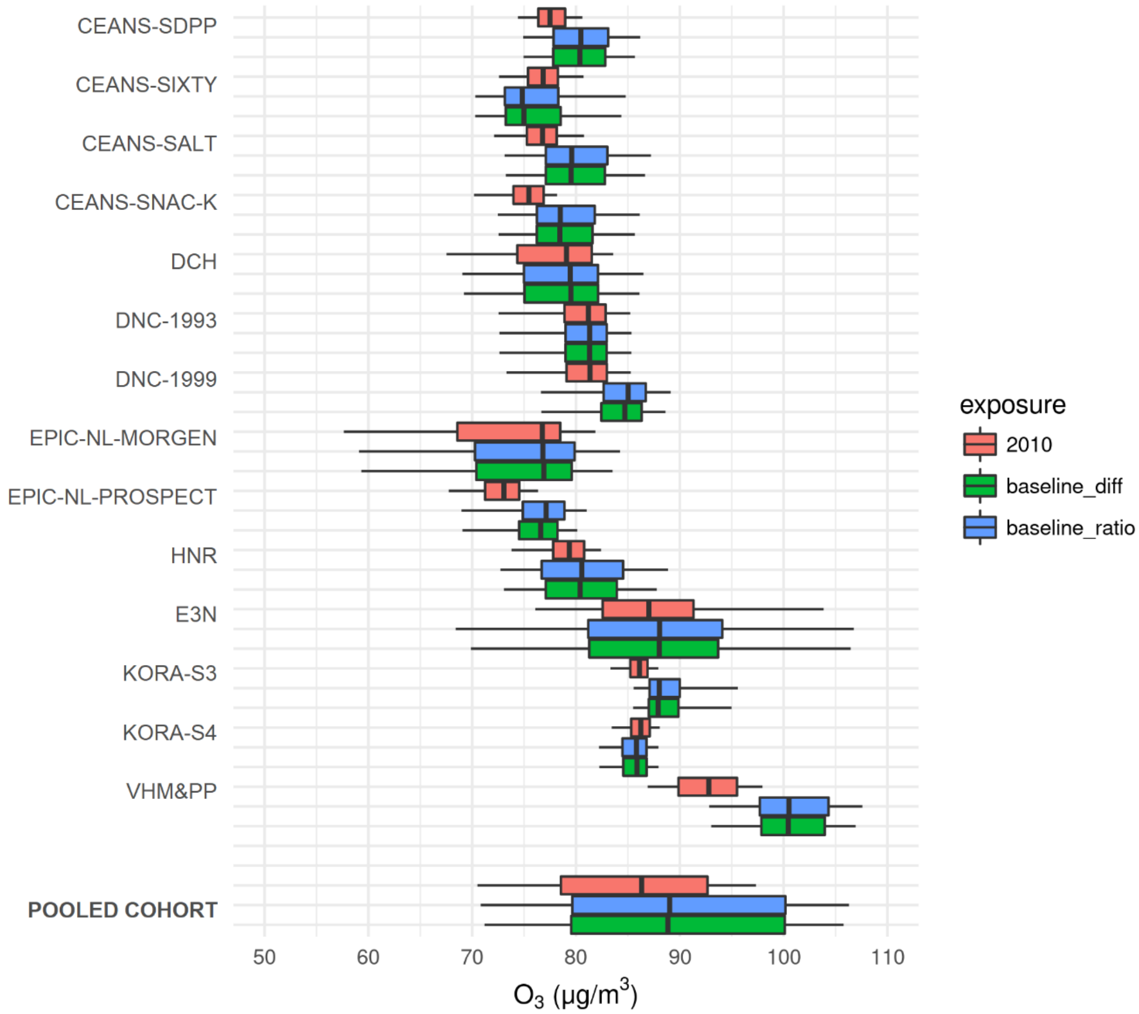


Table S9 Hazard ratios for associations between air pollution and natural mortality using **baseline year exposure**

Pollutant	Main model HR[a]	Back-extrapolated baseline exposure (ratio method)	Back-extrapolated baseline exposure (difference method)
PM2.5	1.130 (1.106, 1.155)	1.048 (1.038, 1.059)	1.058 (1.042, 1.075)
NO_2	1.086 (1.070, 1.102)	1.056 (1.045, 1.067)	1.082 (1.067, 1.098)
BC	1.081 (1.065, 1.098)	1.046 (1.034, 1.058)	1.072 (1.057, 1.088)
O_3	0.896 (0.878, 0.914)	0.918 (0.902, 0.935)	0.916 (0.899, 0.933)

[a] Main model 3 restricted to subjects available in the back-extrapolated baseline exposure analysis (N=325,342). HR (95% confidence interval) presented for the following increments: $PM_{2.5}$ – 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Table S10 Hazard ratios for associations between air pollution and natural mortality in time-varying analyses: **time-varying exposure including residential mobility and strata for 1- or 5-year time periods to adjust for time trends in mortality and pollution**

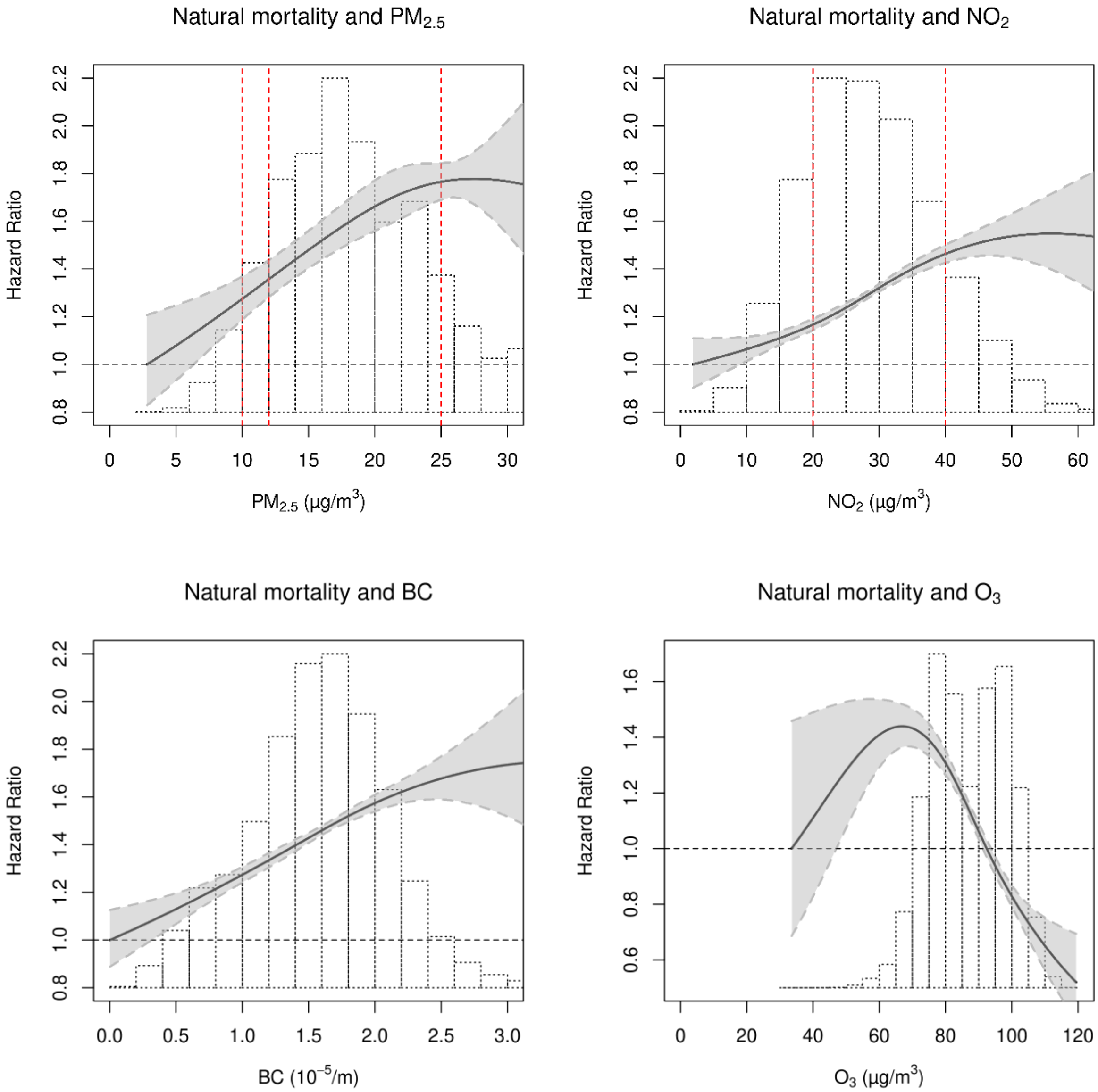
Pollutant	Main model HR, reduced set of cohorts[a]	Strata for 1 year[b] (ratio method)	Strata for 1 year (difference method)	Strata for 5 year (ratio method)	Strata for 5 year (difference method)
PM2.5	1.123 (1.090, 1.157)	1.123 (1.093, 1.153)	1.136 (1.103, 1.170)	1.085 (1.061, 1.109)	1.081 (1.057, 1.107)
NO_2	1.104 (1.083, 1.126)	1.109 (1.089, 1.130)	1.112 (1.091, 1.133)	1.112 (1.093, 1.133)	1.116 (1.095, 1.138)
BC	1.098 (1.076, 1.120)	1.108 (1.086, 1.131)	1.103 (1.081, 1.124)	1.085 (1.064, 1.107)	1.102 (1.081, 1.124)
O_3	0.887 (0.864, 0.910)	0.932 (0.920, 0.945)	0.932 (0.920, 0.944)	0.897 (0.887, 0.907)	0.895 (0.885, 0.906)

[a] Main model 3 restricted to subjects available in the time-varying analysis (N=185,585).

[b] The 1-year and 5-year strata refer to calendar time periods we used to adjust for time trends inmortality.

HR (95% confidence interval) presented for the following increments: $PM_{2.5}$ – 5 μg/m^3, NO_2 – 10 μg/m^3, BC – 0.5*10-5/m, O_3 – 10 μg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Figure S15 Natural cubic splines (3 degrees of freedom) for associations between **time-varying exposure and natural mortality**



Red dotted lines are air quality limit and guideline values. X-axis truncated at 30, 60, 3 and 120 µg/m^3 for PM2.5, NO_2, BC and O_3. HR=1 for minimum pollution exposure.

Table S11 Hazard ratios for associations between air pollution and natural mortality: **alternative confounder adjustment**

Additional confounder analysis	Confounder model	Cohorts	PM2.5	NO_2	BC	O_3
	Model 1	All (N=325,367)	1.152 (1.127, 1.177)	1.113 (1.097, 1.129)	1.113 (1.096, 1.129)	0.844 (0.828, 0.862)
Smoking	Model 1 **+ smoking status**	All (N=325,367)	1.138 (1.114, 1.163)	1.089 (1.073, 1.104)	1.089 (1.073, 1.105)	0.872 (0.855, 0.890)
	Model 1 + smoking status **+ smoking intensity (linear)**	All (N=325,367)	1.139 (1.115, 1.164)	1.088 (1.073, 1.104)	1.088 (1.072, 1.104)	0.876 (0.858, 0.893)
	Model 1 + smoking status + smoking intensity (linear) **+ smoking intensity (squared)**	All (N=325,367)	1.139 (1.114, 1.163)	1.088 (1.072, 1.103)	1.088 (1.072, 1.104)	0.875 (0.857, 0.892)
	Model 1 + smoking status + smoking intensity (linear) + smoking intensity (squared) **+ smoking duration**	All (N=325,367)	1.136 (1.112, 1.160)	1.086 (1.071, 1.102)	1.086 (1.070, 1.102)	0.877 (0.860, 0.895)
BMI	Model 1 + smoking status + smoking intensity (linear) + smoking intensity (squared) + smoking duration **+ BMI**	All (N=325,367)	1.131 (1.107, 1.156)	1.085 (1.070, 1.101)	1.085 (1.069, 1.101)	0.881 (0.863, 0.899)
Marital status	Model 1 + smoking status + smoking intensity (linear) + smoking intensity (squared) + smoking duration + BMI **+ marital status**	All (N=325,367)	1.118 (1.095, 1.143)	1.067 (1.052, 1.083)	1.067 (1.051, 1.083)	0.901 (0.883, 0.920)

Table S11 continued.

Additional confounder analysis	Confounder model	Cohorts	PM2.5	NO_2	BC	O_3
Employment	Model 1 + smoking status + smoking intensity (linear) + smoking intensity (squared) + smoking duration + BMI + marital status + **employment = Model 2**	All (N=325,367)	1.121 (1.097, 1.146)	1.070 (1.055, 1.086)	1.069 (1.053, 1.085)	0.899 (0.881, 0.918)
	Main model (model 3)	All (N=325,367)	1.130 (1.106, 1.155)	1.086 (1.070, 1.102)	1.081 (1.065, 1.098)	0.896 (0.878, 0.914)
Education	Main model	- VHM (N=179,773)	1.131 (1.085, 1.179)	1.058 (1.039, 1.078)	1.051 (1.031, 1.071)	0.954 (0.930, 0.979)
	Main model + education		1.132 (1.086, 1.180)	1.059 (1.040, 1.079)	1.052 (1.032, 1.072)	0.955 (0.931, 0.980)
Smoking in former smokers	Main model	- VHM (N=180,984)	1.129 (1.083, 1.177)	1.058 (1.038, 1.078)	1.051 (1.031, 1.071)	0.954 (0.930, 0.979)
	Main model + smoking		1.123 (1.078, 1.171)	1.055 (1.035, 1.075)	1.048 (1.028, 1.068)	0.957 (0.933, 0.981)
Fruit (tertile)	Main model	- CEANS, DNC, HNR, KORA, VHM(N=125,353)	1.113 (1.061, 1.166)	1.060 (1.036, 1.085)	1.046 (1.022, 1.070)	0.957 (0.930, 0.984)
	Main model + fruit		1.112 (1.060, 1.165)	1.060 (1.036, 1.084)	1.045 (1.022, 1.069)	0.957 (0.930, 0.985)
Fruit (elapse)	Main model	- CEANS-SALT, VHM(N=173,710)	1.128 (1.082, 1.176)	1.058 (1.038, 1.078)	1.050 (1.030, 1.070)	0.956 (0.932, 0.982)
	Main model + fruit		1.127 (1.081, 1.175)	1.057 (1.037, 1.078)	1.050 (1.030, 1.070)	0.957 (0.932, 0.982)

Table S11 continued.

Additional confounder analysis	Confounder model	Cohorts	PM2.5	NO_2	BC	O_3
Fruit (cat)	Main model	- CEANS-SALT, E3N, EPIC_NL, VHM (N=101,994)	1.177 (1.115, 1.243)	1.074 (1.050, 1.099)	1.070 (1.046, 1.095)	0.946 (0.914, 0.979)
	Main model + fruit		1.174 (1.111, 1.240)	1.072 (1.048, 1.097)	1.069 (1.045, 1.094)	0.948 (0.916, 0.981)
Total vegetables	Main model	- CEANS, DNC, HNR, KORA, VHM (N=125,353)	1.113 (1.061, 1.166)	1.060 (1.036, 1.085)	1.046 (1.022, 1.070)	0.957 (0.930, 0.984)
	Main model + total vegetables		1.110 (1.058, 1.163)	1.057 (1.033, 1.082)	1.043 (1.019, 1.067)	0.960 (0.933, 0.987)
Raw vegetables (tertile)	Main model	- CEANS, DNC, EPIC_NL, HNR, KORA, VHM(N=92,607)	1.101 (1.048, 1.156)	1.060 (1.033, 1.087)	1.046 (1.021, 1.072)	0.955 (0.925, 0.986)
	Main model + vegetables		1.092 (1.039, 1.147)	1.053 (1.027, 1.080)	1.039 (1.014, 1.065)	0.957 (0.927, 0.989)
Raw vegetables (elapse)	Main model	- CEANS, DNC, EPIC_NL, VHM (N=102,116)	1.102 (1.050, 1.157)	1.059 (1.033, 1.085)	1.046 (1.022, 1.071)	0.949 (0.920, 0.980)
	Main model + vegetables		1.094 (1.042, 1.148)	1.053 (1.028, 1.079)	1.040 (1.015, 1.065)	0.952 (0.922, 0.983)
Raw vegetables (cat)	Main model	- CEANS, DNC, E3N, EPIC_NL, VHM (N=63,139)	1.162 (1.087, 1.243)	1.084 (1.052, 1.117)	1.071 (1.041, 1.102)	0.939 (0.901, 0.978)
	Main model + vegetables		1.147 (1.073, 1.227)	1.074 (1.043, 1.107)	1.060 (1.030, 1.090)	0.944 (0.906, 0.983)
Meat (tertile)	Main model	- CEANS, DNC, HNR, KORA, VHM (N=125,353)	1.113 (1.061, 1.166)	1.060 (1.036, 1.085)	1.046 (1.022, 1.070)	0.957 (0.930, 0.984)
	Main model + meat		1.113 (1.062, 1.167)	1.061 (1.037, 1.085)	1.046 (1.023, 1.070)	0.956 (0.929, 0.984)
Meat (elapse)	Main model	- CEANS-SALT, CEANS-SDPP, CEANS-SIXTY,DNC, VHM (N=137,242)	1.121 (1.071, 1.175)	1.061 (1.038, 1.085)	1.048 (1.025, 1.071)	0.949 (0.923, 0.976)
	Main model + meat		1.122 (1.071, 1.175)	1.062 (1.038, 1.085)	1.048 (1.026, 1.072)	0.949 (0.922, 0.976)

Table S11 continued.

Additional confounder analysis	Confounder model	Cohorts	PM2.5	NO_2	BC	O_3
Meat (cat)	Main model	- CEANS-SALT, CEANS-SDPP, CEANS-SIXTY, DNC, E3N, EPIC_NL, VHM (N=65,485)	1.185 (1.109, 1.265)	1.091 (1.059, 1.123)	1.077 (1.047, 1.108)	0.928 (0.892, 0.966)
	Main model + meat		1.183 (1.108, 1.264)	1.090 (1.059, 1.122)	1.077 (1.047, 1.108)	0.929 (0.893, 0.967)
Alcohol	Main model	- CEANS-SIXTY, CEANS-SNACK, VHM (N=171,523)	1.119 (1.073, 1.168)	1.056 (1.035, 1.076)	1.047 (1.027, 1.068)	0.959 (0.934, 0.984)
	Main model + alcohl		1.120 (1.074, 1.169)	1.055 (1.035, 1.076)	1.047 (1.026, 1.067)	0.958 (0.933, 0.983)
Occupational status	Main model	- DCH (N=271,720)	1.111 (1.086, 1.137)	1.068 (1.049, 1.086)	1.066 (1.047, 1.086)	0.906 (0.884, 0.929)
	Main model + Occupational Status		1.110 (1.085, 1.136)	1.068 (1.049, 1.087)	1.066 (1.047, 1.086)	0.907 (0.884, 0.929)
Blue collar job	Main model	- DCH, E3N, EPIC_NL, HNR (N=181,302)	1.124 (1.096, 1.153)	1.090 (1.067, 1.113)	1.095 (1.071, 1.119)	0.863 (0.835, 0.891)
	Main model + Collar Blue		1.125 (1.096, 1.154)	1.098 (1.075, 1.121)	1.100 (1.076, 1.125)	0.855 (0.828, 0.883)
Neighborhood unemployment rate	Main model	- CEANS (N=304,536)	1.128 (1.103, 1.152)	1.086 (1.070, 1.103)	1.080 (1.063, 1.097)	0.897 (0.879, 0.915)
	Main model + Neighborhood unemployment rate		1.127 (1.103, 1.152)	1.084 (1.068, 1.101)	1.078 (1.062, 1.095)	0.899 (0.880, 0.917)
Neighborhood low educational level rate	Main model	- EPIC_NL, HNR, KORA (N=282,908)	1.131 (1.107, 1.156)	1.092 (1.075, 1.109)	1.088 (1.071, 1.105)	0.885 (0.866, 0.904)
	Main model + Neighborhood low educational level rate		1.132 (1.108, 1.157)	1.096 (1.079, 1.113)	1.092 (1.075, 1.110)	0.880 (0.861, 0.900)

Table S11 continued.

Additional confounder analysis	Confounder model	Cohorts	PM2.5	NO_2	BC	O_3
Neighborhood high educational level rate	Main model	- EPIC_NL, HNR, KORA (N=282,908)	1.131 (1.107, 1.156)	1.092 (1.075, 1.109)	1.088 (1.071, 1.105)	0.885 (0.866, 0.904)
	Main model + Neighborhood high educational level rate		1.133 (1.109, 1.158)	1.098 (1.081, 1.115)	1.094 (1.077, 1.112)	0.879 (0.860, 0.899)
Neighborhood ethnicity	Main model	- CEANS, HNR, KORA (N=295,078)	1.128 (1.104, 1.153)	1.088 (1.071, 1.105)	1.081 (1.065, 1.098)	0.897 (0.879, 0.916)
	Main model + Neighborhood Ethnicity		1.120 (1.095, 1.145)	1.083 (1.064, 1.101)	1.074 (1.056, 1.092)	0.905 (0.886, 0.925)

HR (95% confidence interval) presented for the following increments: $PM_{2.5}$ – 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Figure S16 Hazard ratios for associations between air pollution and natural mortality: **impact of dropping one cohort at a time**

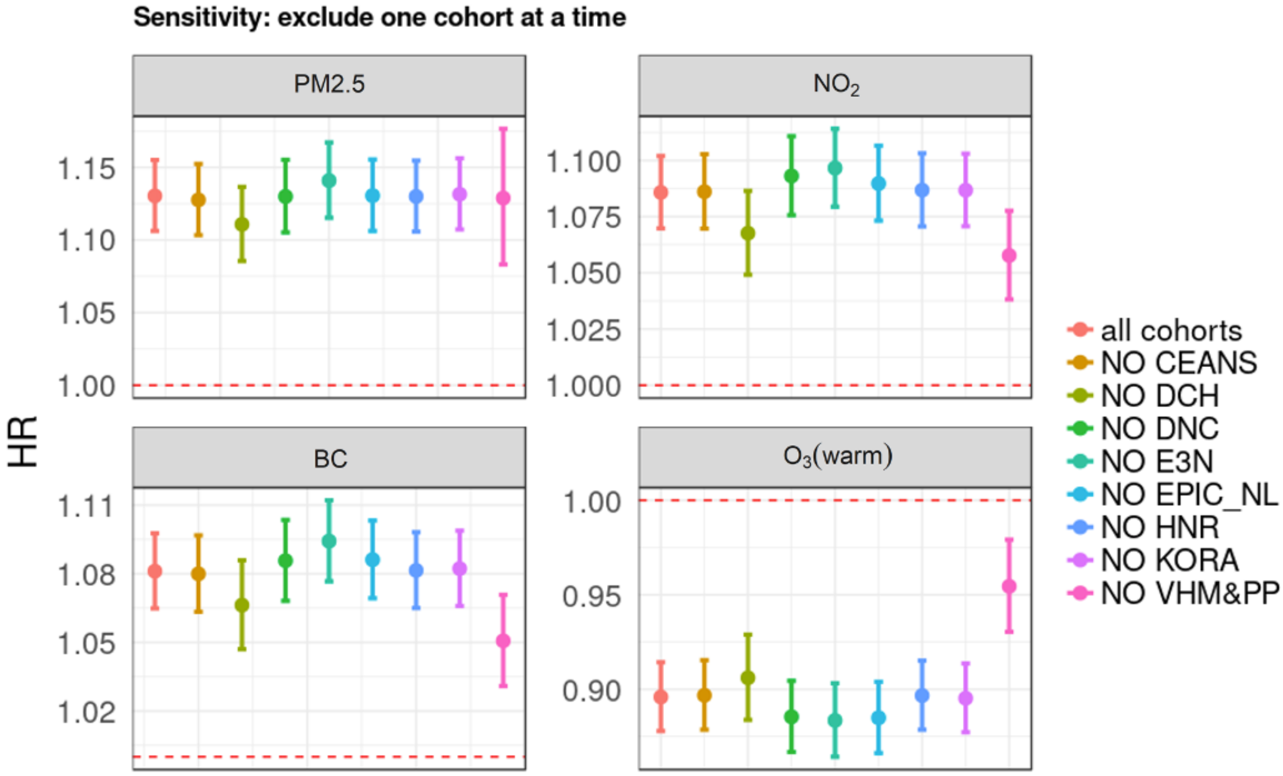


Table S12 Hazard ratios for associations between air pollution and natural and cause-specific mortality: **additional adjustment for road-traffic noise**

Pollutant	Main model	Additional adjustment for road-traffic noise
Natural mortality		
PM2.5	1.176(1.115, 1.241)	1.156(1.093, 1.223)
NO_2	1.073(1.050, 1.097)	1.068(1.042, 1.095)
BC	1.071(1.047, 1.096)	1.064(1.038, 1.091)
O_3	0.942(0.911, 0.974)	0.958(0.924, 0.993)
Cardiovascular mortality		
PM2.5	1.127 (1.006, 1.262)	1.105 (0.980, 1.245)
NO_2	1.060 (1.013, 1.110)	1.053 (1.000, 1.110)
BC	1.051 (1.003, 1.103)	1.041 (0.988, 1.098)
O_3	0.945 (0.881, 1.013)	0.961 (0.891, 1.036)
Cerebrovascular mortality		
PM2.5	1.172 (0.944, 1.456)	1.149 (0.915, 1.443)
NO_2	1.039 (0.951, 1.134)	1.023 (0.927, 1.130)
BC	1.039 (0.949, 1.138)	1.025 (0.927, 1.132)
O_3	0.905 (0.791, 1.034)	0.916 (0.793, 1.059)
Ischemic heart disease mortality		
PM2.5	0.940 (0.786, 1.124)	0.949 (0.786, 1.146)
NO_2	1.000 (0.931, 1.075)	1.012 (0.933, 1.098)
BC	0.995 (0.923, 1.071)	1.004 (0.924, 1.090)
O_3	1.000 (0.896, 1.117)	0.988 (0.877, 1.113)
Diabetes mortality		
PM2.5	1.151 (0.759, 1.746)	1.096 (0.708, 1.696)
NO_2	1.154 (0.964, 1.380)	1.143 (0.933, 1.400)
BC	1.139 (0.953, 1.361)	1.123 (0.922, 1.369)
O_3	0.949 (0.735, 1.226)	0.991 (0.751, 1.307)

Table S12 continued.

Pollutant	Main model	Additional adjustment for road-traffic noise
Cardio-metabolic mortality		
PM2.5	1.132 (1.015, 1.263)	1.108 (0.987, 1.243)
NO_2	1.067 (1.021, 1.116)	1.060 (1.008, 1.115)
BC	1.058 (1.011, 1.108)	1.048 (0.996, 1.103)
O_3	0.942 (0.881, 1.008)	0.959 (0.892, 1.032)

N=109,021; road-traffic noise available for CEANS, DCH, DNC (using the Nordic Prediction method), HNR and KORA(using the German VDUS/RLS-90 method); HR (95% confidence interval) presented for the following increments: $PM_{2.5}$– 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Table S13 Hazard ratios for associations between air pollution and natural mortality in **two-pollutant models, without VHM&PP cohort**

Pollutant	Single pollutant HR	HR adjusted for PM2.5	HR adjusted for NO2	HR adjusted for BC	HR adjusted for O_3
PM2.5	1.129 (1.083, 1.177)	NA	1.071 (1.013, 1.133)	1.092 (1.036, 1.152)	1.115 (1.065, 1.168)
NO_2	1.058 (1.038, 1.078)	1.036 (1.010, 1.062)	NA	1.064 (1.021, 1.109)	1.056 (1.032, 1.080)
BC	1.051 (1.031, 1.071)	1.024 (1.000, 1.050)	0.993 (0.952, 1.036)	NA	1.044 (1.021, 1.067)
O_3	0.954 (0.930, 0.979)	0.983 (0.955, 1.011)	0.995 (0.965, 1.027)	0.982 (0.954, 1.011)	NA

NA=not applicable; Two-pollutant models of BC and NO_2 are difficult to interpret because of high correlation between BC and NO_2.

N=325,367; HR (95% confidence interval) presented for the following increments: PM2.5 – 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighborhood-level mean income.

Table S14 Hazard ratios for associations between air pollution and natural mortality in **two-pollutant models, without VHM&PP cohort and adjusting for road-traffic noise**

Pollutant	Single pollutant HR	HR adjusted for PM2.5	HR adjusted for NO2	HR adjusted for BC	HR adjusted for O_3
PM2.5	1.156 (1.093, 1.223)	NA	1.090 (1.015, 1.171)	1.101 (1.028, 1.179)	1.151 (1.083, 1.224)
NO_2	1.068 (1.042, 1.095)	1.043 (1.011, 1.077)	NA	1.048 (0.998, 1.100)	1.069 (1.039, 1.100)
BC	1.064 (1.038, 1.091)	1.039 (1.008, 1.071)	1.022 (0.974, 1.073)	NA	1.062 (1.034, 1.092)
O_3	0.958 (0.924, 0.993)	0.992 (0.954, 1.032)	1.003 (0.963, 1.045)	0.995 (0.956, 1.035)	NA

NA=not applicable; Two-pollutant models of BC and NO_2 are difficult to interpret because of high correlation between BC and NO_2.

N=325,367; HR (95% confidence interval) presented for the following increments: PM2.5 – 5 $\mu g/m^3$, NO_2 – 10 $\mu g/m^3$, BC – 0.5*10-5/m, O_3 – 10 $\mu g/m^3$; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighborhood-level mean income. Noise was not available in VHM&PP cohort.

Table S15 Hazard ratios for associations between air pollution and natural mortality: **multiple imputation**

Pollutant	Main model	Main model with multiple imputation
PM2.5	1.13 (1.11, 1.16)	1.12 (1.10, 1.15)
NO_2	1.09 (1.07, 1.10)	1.09 (1.07, 1.10)
BC	1.08 (1.06, 1.10)	1.08 (1.06, 1.09)
O_3	0.90 (0.88, 0.91)	0.90 (0.88, 0.91)

HR (95% confidence interval) presented for the following increments: $PM_{2.5}$– 5 µg/m^3, NO_2 – 10 µg/m^3, BC – 0.5*10-5/m, O_3 – 10 µg/m^3; main model adjusted for cohort id, age, sex, year of baseline visit, smoking (status, duration, intensity, intensity^2), BMI, marital status, employment status and 2001 neighbourhood-level mean income.

Figure S17 Effect modification for associations between air pollution and natural mortality

Baseline characters	Numbers	P valueϕ
Sex		
Female	214,900	$PM_{2.5}$: <0.01; NO_2: <0.01
Male	110,467	
Age, years		
<65	298,496	$PM_{2.5}$: 0.07; NO_2: <0.01
≥65	26,871	
Smoking status		
Current smoker	78,584	
Previous smoker	59,488	$PM_{2.5}$: 0.01; NO_2: 0.94
Never smoker	187,295	
BMI, kg/m²		
<18.5	7,499	
18.5-24.9	177,053	$PM_{2.5}$: 0.75; NO_2: 0.35
25.0-29.9	105,287	
≥30.0	35,528	

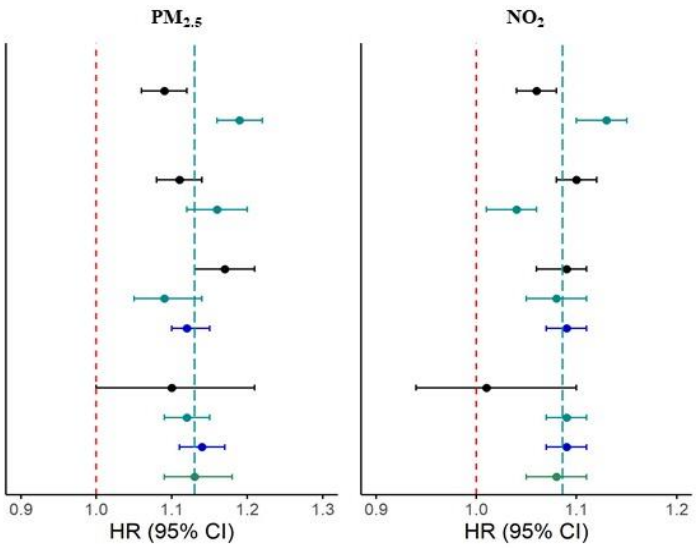


Table S16 Comparison of findings for natural mortality with recent North American administrative cohorts, ESCAPE and recent meta-analyses estimates

	HR PM2.5 per 10 µg/m³	**HR NO_2 per 10 µg/m³**	**HR O_3 per 10 µg/m³**
ELAPSE *(current study)*	1.28 (1.22, 1.33)	1.09 (1.07, 1.10)	0.90 (0.88, 0.91)
MAPLE CanCHEC *(Crouse et al., 2015; Pinault et al., 2017)*	1.05 (1.04, 1.07)	1.004 (1.002, 1.006)	1.036 (1.033, 1.038)
MAPLE CCHS *(Pinault et al., 2016)*	1.11 (1.04, 1.18)	1.024 (1.016, 1.040)	1.025 (1.015, 1.034)
MEDICARE *(Di et al., 2017)*	1.084 (1.081, 1.086)		1.012 (1.011, 1.012)
ESCAPE *(Beelen et al., 2011)*	1.14 (1.04, 1.26)	1.01 (0.99, 1.03)	
Pope et al., 2020	1.08 (1.06, 1.11)		
Chen and Hoek, 2020	1.08 (1.06, 1.09)		
Huangfu and Atkinson, 2020		1.02 (1.01, 1.04)	1.01 (1.00, 1.02)
Raaschou-Nielsen et al., 2020	1.08 (1.04, 1.13)	1.05 (1.04, 1.06)	0.96 (0.95, 0.97)

References:

Beelen R, Raaschou-Nielsen O, Stafoggia M, et al. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 2014;383:785–95.

Chen J and Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ Int 2020:105974.

Crouse DL, Peters PA, Hystad P, et al. Ambient PM 2.5, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 2015;123(11):1180–6.

Di Q, Wang Y, Zanobetti A, et al. Air pollution and mortality in the medicare population. N Engl J Med 2017;376:2513–22.

Pinault L, Tjepkema M, Crouse DL, et al. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. Environ Heal 2016;15:18.

Pinault LL, Weichenthal S, Crouse DL, et al. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ Res 2017;159:406–15.

Pope CA, Coleman N, Pond ZA, Burnett RT. Fine particulate air pollution and human mortality: 25+ years of cohort studies. Environ Res 2020;183:108924.

Raaschou-Nielsen O, Thorsteinson E, Antonsen S, et al. Long-term exposure to air pollution and mortality in the Danish population a nationwide study. EClinicalMedicine 2020;28:100605.