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Supplemental Material

Long-Term Exposure to Low-Level PM$_{2.5}$ and Mortality: Investigation of Heterogeneity by Harmonizing Analyses in Large Cohort Studies in Canada, United States, and Europe

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Table S1. Individual- and area-level covariates included in the main Model 4 in each cohort

	Stacked CanCHEC	Medicare[1]	Belgian	Danish	Dutch	Norwegian	Roman	Swiss
Individual-level covariates								
Age	strata[2]	strata[2]	time axis	time axis	time axis	time axis	time axis	time axis
Sex	strata	strata	strata	strata	strata	strata	strata	strata
Follow-up year	time axis	strata	strata	strata	strata	strata	strata	strata
Variable representing race/ethnicity	Immigrant status, visible minority status, and indigenous identity (categorical)	Race/ethnicity (strata)	Country origin (categorical)	Country origin (categorical)	Country origin (categorical)	-	-	Nationality, mother tongue (categorical)
Variable representing SES	Income (quintiles)	Medicaid eligibility (strata)	Education (categorical)	Income (deciles)	Income (deciles)	Income (quartiles)	Education (categorical)	Education (categorical)
Area-level covariates								
Composite SES index	Linear[3]	-	-	-	linear[4]	-	quintiles[5]	Linear[6]
(Household) income	-	linear	linear	linear	linear	-	deciles	-
Median house value	-	linear	-	-	-	-	-	-
Proportion of residents in poverty	-	linear	-	-	-	Linear	-	-
Proportion of residents that own their house	-	linear	-	-	-	-	-	-
Low/high education rate	-	linear	linear	linear	-	linear	linear	linear
Unemployment rate	-	-	linear	linear	linear	linear	linear	linear
Non-western ethnic rate	-	-	linear	-	linear	-	-	-
Number of regional/airshed indicators in the cohort	6	4	3	5	12	5	NA	7

[1] A Cox regression-equivalent Poisson formulation was applied; [2] 5-year categories; [3] Composite index of instability, material deprivation, dependency, and ethnic concentration at census tract level in cities or census subdivision level outside of cities; [4] Composite index of education, income and paid occupation at neighborhood and regional levels; [5] Composite index of education, occupation, house ownership, family composition, crowding, and immigrant status at neighborhood level; [6] Composite index of median rent, education, occupation, and crowding at neighborhood and regional levels

Table S2. Characteristics of the full study populations in the stacked CanCHEC and ELAPSE cohorts

		Stacked CanCHEC	Belgian	Danish	Dutch	Norwegian	Roman	Swiss
Follow-up	*Start-end*	1991-2016	2001-2011	2000-2015	2008-2012	2001-2016	2001-2015	2000-2014
Persons at risk	*N*	6,144,200[a]	5,474,548	3,079,709	10,187,024	2,119,512	1,263,712	3,987,024
Person-years at risk	*N*	94,736,400[a]	51,874,182	42,537,377	49,104,281	29,873,933	15,301,265	50,355,026
All-cause mortality	*rate*1000 py*	11.2	14.6	17.5	12.5	17.0	16.1	13.8
Natural mortality[b]	*rate*1000 py*	10.6	13.6	16.8	12.0	16.1	15.4	13.1
Sex (%)	*Males*							
	Females	52.0	49.4	51.7	51.4	51.0	54.5	52.3
Baseline age (years)	*Mean ± SD*	44.5 ± 13.2	52.6 ± 15.2	53.0 ± 15.2	53.0 ± 14.8	53.9 ± 15.9	55.1 ± 15.4	53.1 ± 15.2
PM$_{2.5}$ exposure during follow-up ($\mu g/m^3$)	*Mean ± SD*	7.7 ± 2.5	15.4 ± 1.5	9.7 ± 1.5	15.7 ± 1.4	6.7 ± 1.6	17.6 ± 1.2	15.9 ± 3.0
Individual-level SES covariates and ethnicity								
Country origin/ immigration status (%)	*Local/nonimmigrants*	83.5	96.9	94.3	83.0	-	-	-
	Foreign/immigrants		3.1	5.7	17.0	-	-	-
Nationality (%)	*Swiss*	-	-	-	-	-	-	83.3
	Non-Swiss	-	-	-	-	-	-	16.7
Mother tongue (%)	*German and Rhaeto-Romansch*	-	-	-	-	-	-	65.5
	French	-	-	-	-	-	-	19.4
	Italian	-	-	-	-	-	-	7.4
	other	-	-	-	-	-	-	7.7
Visible minority status (%)	*Yes*	7.1	-	-	-	-	-	-
	No	92.9	-	-	-	-	-	-
Indigenous identity (%)	*Yes*	3.3	-	-	-	-	-	-
	No	96.7	-	-	-	-	-	-
(Household) income	*Levels*	Quintiles	-	Deciles	Deciles	Quartiles	-	-
Educational level (%)	*Primary or below*	28.2	23.8	-	-	30.7	24.9	24.8
	Secondary	55.9	51.9	-	-	45.9	58.8[c]	52.9
	Tertiary	15.7	24.3	-	-	23.4	16.2	22.3
Marital status (%)	*Single*	12.8	12.3	-	17.9	17.6	15.3	13.3
	Married	75.8	68.3	-	63.8	59.5	66.3	69.8
	Divorced	7.6	9.9	-	10.2	12.4	7	8.5
	Widowed	3.5	9.5	-	8.0	10.5	11.4	8.4
Employment status (%)	*Employed*	70.2	53.3	59.7	-	66	45.8	60.8
	Unemployed	5.3	5.1	2.6	-	1.2	5	2
	Homemaker	-	8.5	-	-	-	21	14.7
	Retired	24.0[d]	33.2	37.7[e]	-	32.8	23.5	22.4

- Not available

[a] Rounded to nearest 100 for confidentiality

[b] Natural mortality was defined by the International Classification of Diseases, 9th revision (ICD-9) or 10th revision (ICD-10) codes: ICD-9: 1–779; ICD-10: A00–R99

[c] Grouped junior high school and high school

[d] Employment status has three classes in CanCHEC: employed, unemployed, and not in the labor force ((i.e., persons who left on disability, had retired, or had never worked)

[e] Employment status has three classes in the Danish cohort: employed, unemployed, and pensioner (i.e., retired, sick, cash support, student, pension, or others)

Table S3. Comparison of different exposure assessment methods applied in cohorts

	Harmonized exposure[1]		Original exposure in published reports	
	N[2]	HR (95% CI)	N[2]	HR (95% CI)
Medicare	74,493,754	**1.025 (1.021, 1.029)**	68,503,979	**1.032 (1.025, 1.040)[3]**
Overall ELAPSE	26,111,529	**1.050 (1.020, 1.081)**	26,413,334	**1.042 (1.010, 1.075)[4]**
Belgian	5,474,548	1.022 (1.014, 1.029)	5,384,017	1.005 (0.995, 1.015)[5]
Danish	3,079,709	1.117 (1.104, 1.129)	3,083,227	1.088 (1.080, 1.096)[5]
Dutch	10,187,024	1.069 (1.054, 1.085)	10,386,353	1.005 (0.995, 1.015)[5]
Norwegian	2,119,512	1.040 (1.031, 1.050)	2,309,001	1.094 (1.084, 1.104)[5]
Rome	1,263,712	1.049 (1.030, 1.069)	1,263,712	1.047 (1.023, 1.072)[5]
Swiss	3,987,024	1.008 (1.002, 1.013)	3,987,024	1.017 (1.012, 1.023)[5]

Hazard ratios (HRs) and 95% confidence intervals (CIs) are associated with a 5 $\mu g/m^3$ increase in $PM_{2.5}$ exposure

[1] Harmonized exposure applied in the present study, main Model 4 results for **Medicare** – model adjusted for sex (strata), 5-year age groups (strata), follow-up year (strata), race (strata), Medicaid eligibility (strata), ZIP code level income, median house value, poverty rate, house-owing rate, high education rate, and Census region indicator; additional Model 4 results for natural mortality in the full study population (aged 30+) for European cohorts: **Belgian** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, education, marital status, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, non-western ethnic rate, and regional indicator, **Danish** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, and regional indicator, **Dutch** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, marital status, both neighborhood- and regional level composite SES index, income, unemployment rate, non-western ethnic rate, and regional indicator, **Norwegian** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), income, education, marital status, employment status, both neighborhood- and regional level poverty rate, unemployment rate, low education rate, and regional indicator, **Roman** cohort (additional Model 3) – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), education, marital status, employment status, neighborhood-level income, unemployment rate, low education rate, high education rate, and composite SES index, **Swiss** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), nationality, mother tongue, education, marital status, employment status, both neighborhood- and regional level composite SES index, unemployment rate, low education rate, high education rate, and regional indicator

[2] Complete case analysis was performed in both sets of analyses and thus led to different Ns.

[3] Exposure applied in the **Medicare** report;[1] results from Cox proportional hazards model – model adjusted for follow-up year (time-axis), sex (strata), 5-year age groups (strata), race (strata), Medicaid eligibility (strata), county-level average body mass index and smoking rate, ZIP code level proportion of Hispanic residents, proportion of Black residents, income, median house value, poverty rate, house-owing rate, high education rate, population density, meteorological variables: the summer (June to September) and winter (December to February) averages of maximum daily temperatures and relative humidity, Census region indicator, and indicators for calendar years 2000–2016.

[4] Meta-analytic estimate of six ELAPSE cohorts

[5] Exposure applied in the ELAPSE report;[2] results from time-varying analyses stratified for 1-year, exposure estimated with back-extrapolation using ratio method: **Belgian** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, education, marital status, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, non-western ethnic rate, **Danish** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, **Dutch** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, marital status, both neighborhood- and regional level composite SES index, income, unemployment rate, non-western ethnic rate, **Norwegian** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), income, education, marital status, employment status, both neighborhood- and regional level poverty rate, unemployment rate, low education rate, **Roman** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), education, marital status, employment status, neighborhood-level income, unemployment rate, low education rate, high education rate, and composite SES index, **Swiss** cohort – model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), nationality, mother tongue, education, marital status, employment status, both neighborhood- and regional level composite SES index, unemployment rate, low education rate, high education rate
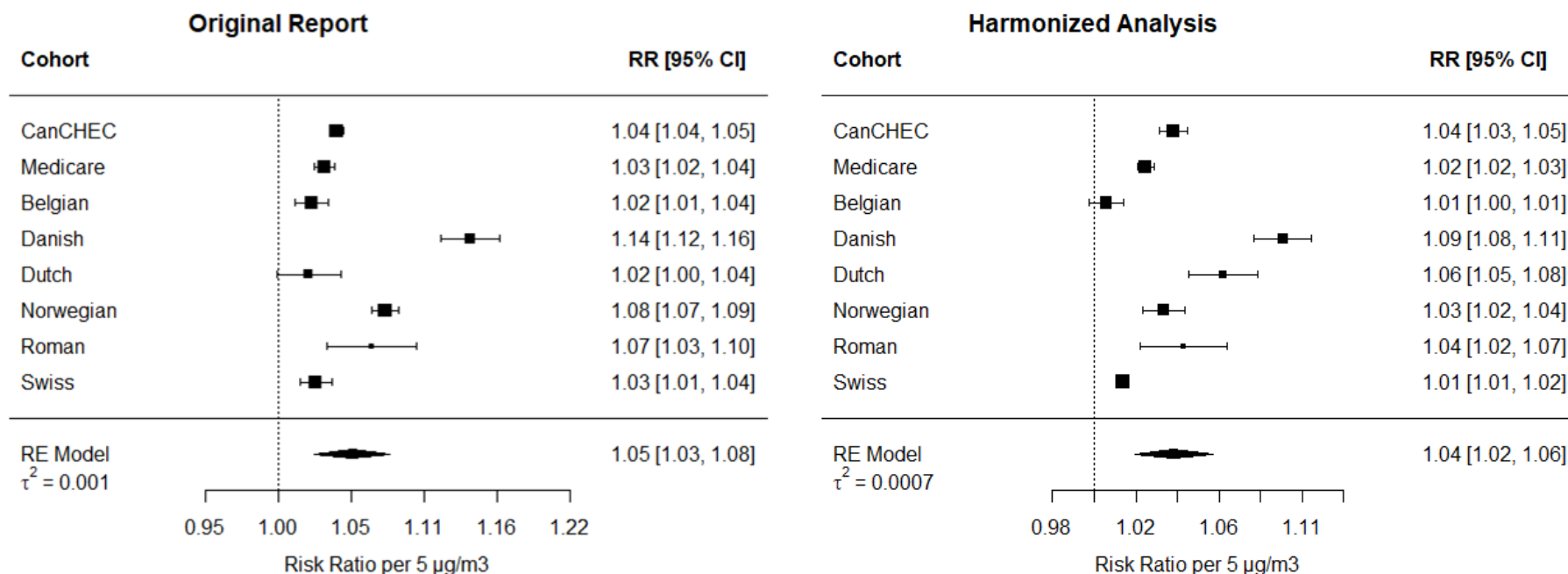
Figure S1. Random-effects meta-analysis of eight cohorts

Risk ratios and 95% confidence intervals are associated with a 5 µg/m^3 increase in PM$_{2.5}$ exposure

Risk ratios from the original report of the eight cohorts can be found in the Health Effects Institute research reports of MAPLE,[3] Medicare,[1] and ELAPSE[2]

Model specification in each cohort in the original report

CanCHEC model adjusted for cohort (strata), sex (strata), 5-year age groups (strata), immigrant status (strata), income, visible minority, indigenous identity, educational attainment, labor- force status, marital status, occupation, and ecological covariates of community size, urban form, neighborhood composite SES index, and airshed indicator; **Medicare** model adjusted for follow-up year (time-axis), sex (strata), 5-year age groups (strata), race (strata), Medicaid eligibility (strata), county-level average body mass index and smoking rate, ZIP code level proportion of Hispanic residents, proportion of Black residents, income, median house value, poverty rate, house-owing rate, high education rate, population density, meteorological variables: the summer (June to September) and winter (December to February) averages of maximum daily temperatures and relative humidity, Census region indicator, and indicators for calendar years 2000–2016; **Belgian** model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, education, marital status, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, non-western ethnic rate, **Danish** model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, employment status, both neighborhood- and regional level income, unemployment rate, low education rate, **Dutch** model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, marital status, both neighborhood- and regional level composite SES index, income, unemployment rate, non-western ethnic rate, **Norwegian** model adjusted for age at follow-up

(time axis), sex (strata), follow-up year (strata), income, education, marital status, employment status, both neighborhood- and regional level poverty rate, unemployment rate, low education rate, **Roman** model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), education, marital status, employment status, neighborhood-level income, unemployment rate, low education rate, high education rate, and composite SES index, **Swiss** model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), nationality, mother tongue, education, marital status, employment status, both neighborhood- and regional level composite SES index, unemployment rate, low education rate, high education rate

Model specification in each cohort in the harmonized analysis

CanCHEC Model adjusted for cohort (strata), sex (strata), 5-year age groups (strata), follow-up year (time axis), income, immigration status, visible minority, indigenous identity, neighborhood composite SES index, and airshed indicator; **Medicare** Model adjusted for sex (strata), 5-year age groups (strata), follow-up year (strata), race (strata), Medicaid eligibility (strata), ZIP code level income, median house value, poverty rate, house-owing rate, high education rate, and Census region indicator; **Belgian** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, education, both neighborhood- and regional level income, unemployment rate, low education rate, non-western ethnic rate, and regional indicator; **Danish** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, both neighborhood- and regional level income, unemployment rate, low education rate, and regional indicator; **Dutch** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, both neighborhood- and regional level composite SES index, income, unemployment rate, non-western ethnic rate, and regional indicator; **Norwegian** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), income, both neighborhood- and regional level poverty rate, unemployment rate, low education rate, and regional indicator; **Roman** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), education, neighborhood-level income, unemployment rate, low education rate, high education rate, and composite SES index; **Swiss** Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), nationality, mother tongue, education, both neighborhood- and regional level composite SES index, unemployment rate, low education rate, high education rate, and regional indicator.
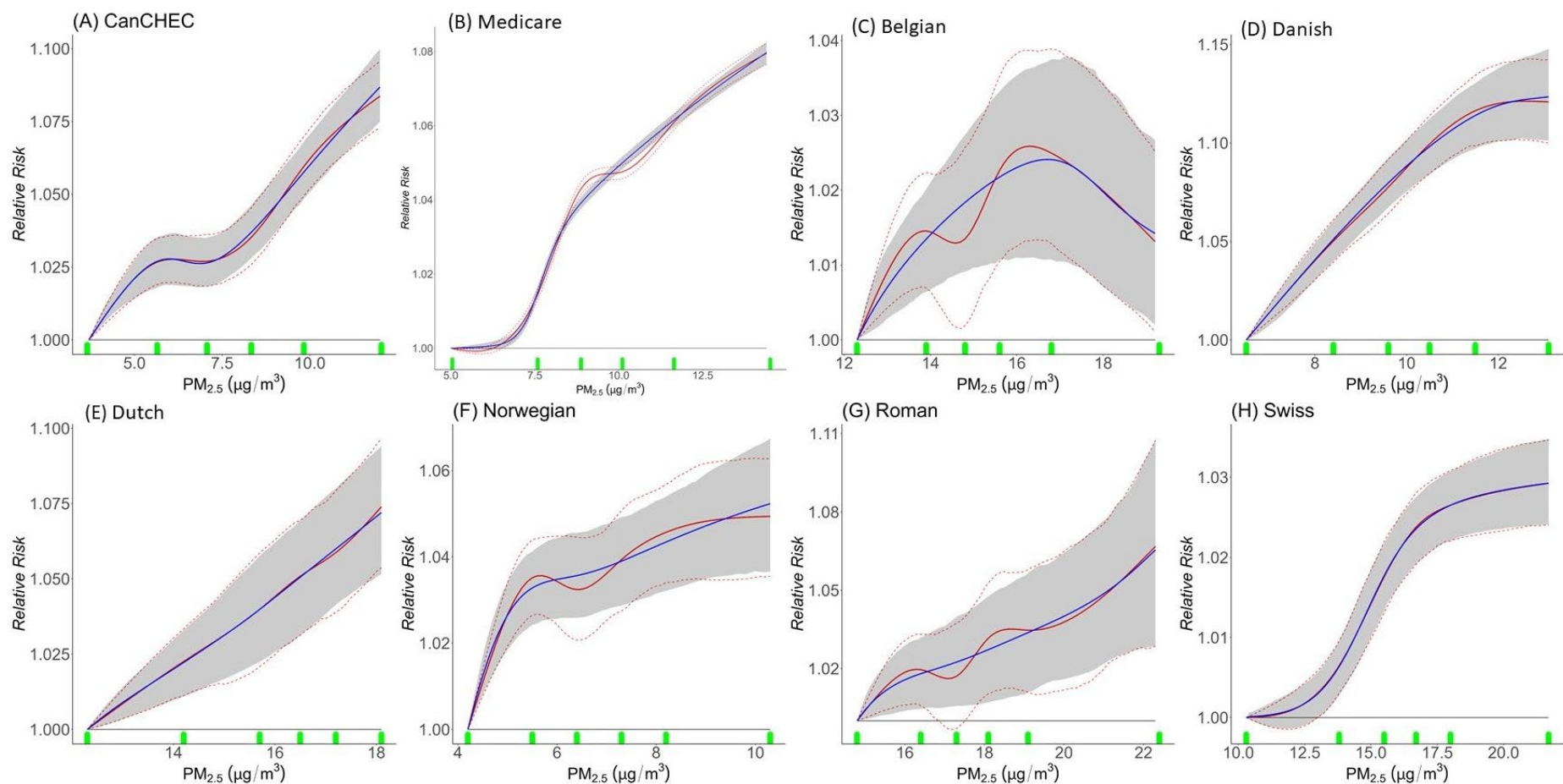
Figure S2. Cohort-specific concentration-response curve for PM$_{2.5}$ exposure and all-cause mortality in study populations aged 65 years and older. eSCHIF (blue solid line with 95% confidence interval indicated by the shaded area) fit to the splines (red solid line with 95% confidence interval indicated by the red dotted lines) with counterfactual level equals the 5th percentile of the cohort-specific PM$_{2.5}$ exposure distributions. Six spline knot values indicated by green tick marks. Curves truncated at the 5th and 95th percentiles of cohort-specific PM$_{2.5}$ exposure distributions (corresponding values specified in Table 1).

Model specification in each cohort in the harmonized analysis

CanCHEC Model adjusted for cohort (strata), sex (strata), 5-year age groups (strata), follow-up year (time axis), income, immigration status, visible minority, indigenous identity, neighborhood composite SES index, and airshed indicator.

Medicare Model adjusted for sex (strata), 5-year age groups (strata), follow-up year (strata), race (strata), Medicaid eligibility (strata), ZIP code level income, median house value, poverty rate, house-owing rate, high education rate, and Census region indicator.

Belgian Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, education, both neighborhood- and regional level income, unemployment rate, low education rate, non-western ethnic rate, and regional indicator.

Danish Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, both neighborhood- and regional level income, unemployment rate, low education rate, and regional indicator.

Dutch Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), country origin, income, both neighborhood- and regional level composite SES index, income, unemployment rate, non-western ethnic rate, and regional indicator.

Norwegian Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), income, both neighborhood- and regional level poverty rate, unemployment rate, low education rate, and regional indicator.

Roman Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), education, neighborhood-level income, unemployment rate, low education rate, high education rate, and composite SES index.

Swiss Model adjusted for age at follow-up (time axis), sex (strata), follow-up year (strata), nationality, mother tongue, education, both neighborhood- and regional level composite SES index, unemployment rate, low education rate, high education rate, and regional indicator.

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