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Early life $PM_{2.5}$ exposure, childhood cognitive ability and mortality between age 11 and 86: A record-linkage life-course study from scotland

Gergő Baranyi [a,*], Lee Williamson [a,b], Zhiqiang Feng [a], Sam Tomlinson [c], Massimo Vieno [d], Chris Dibben [a]

[a] Centre for Research on Environment, Society and Health, School of Geosciences, The University of Edinburgh, Edinburgh, UK
[b] Longitudinal Studies Centre - Scotland, School of GeoSciences, The University of Edinburgh, Edinburgh, UK
[c] UK Centre for Ecology & Hydrology, Library Ave, Bailrigg, Lancaster, UK
[d] UK Centre for Ecology & Hydrology, Bush Estate, Penicuik, UK

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ABSTRACT

Background: Living in areas with high air pollution concentrations is associated with all-cause and cause-specific mortality. Exposure in sensitive developmental periods might be long-lasting but studies with very long follow-up are rare, and mediating pathways between early life exposure and life-course mortality are not fully understood.

Methods: Data were drawn from the Scottish Longitudinal Study Birth Cohort of 1936, a representative record-linkage study comprising 5% of the Scottish population born in 1936. Participants had valid age 11 cognitive ability test scores along with linked mortality data until age 86. Fine particle ($PM_{2.5}$) concentrations estimated with the EMEP4UK atmospheric chemistry transport model were linked to participants' residential address derived from the National Identity Register in 1939 (age 3). Confounder-adjusted Cox regression estimated associations between $PM_{2.5}$ and mortality; regression-based causal mediation analysis explored mediation through childhood cognitive ability.

Results: The final sample consisted of 2734 individuals with 1608 deaths registered during the 1,833,517 person-months at risk follow-up time. Higher early life $PM_{2.5}$ exposure increased the risk of all-cause mortality (HR = 1.03, 95% CI: 1.01–1.04 per 10 μg m^{-3} increment), associations were stronger for mortality between age 65 and 86. $PM_{2.5}$ increased the risk of cancer-related mortality (HR = 1.05, 95% CI: 1.02–1.08), especially for lung cancer among females (HR = 1.11, 95% CI: 1.02–1.21), but not for cardiovascular and respiratory diseases. Higher $PM_{2.5}$ in early life (≥50 μg m^{-3}) was associated with lower childhood cognitive ability, which, in turn, increased the risk of all-cause mortality and mediated 25% of the total associations.

Conclusions: In our life-course study with 75-year of continuous mortality records, we found that exposure to air pollution in early life was associated with higher mortality in late adulthood, and that childhood cognitive ability partly mediated this relationship. Findings suggest that past air pollution concentrations will likely impact health and longevity for decades to come.

1. Introduction

Ambient air pollution poses one of the greatest environmental threats to human health. Fine particulate matter with the aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) is the fifth largest mortality risk factor, with an estimated 4.2 million attributable death and 103 million disability adjusted life years in 2015 (Cohen et al., 2017). Consistent and of high certainty evidence links $PM_{2.5}$ exposure to increased risk of all-cause and cause-specific (e.g., cardiovascular, lung cancer, respiratory) mortality in the general population (Chen and Hoek, 2020; Pope et al., 2020; Liu et al., 2019; Orellano et al., 2020). Large number of studies focussed on the short (from 1 h to 7 days) (Orellano et al., 2020), medium (<10 years) and long-term impacts (<25 years) (Chen and Hoek, 2020) of poor air quality, however, the number of investigations drops when it comes to very-long term (≥25 years) associations (Filleul et al., 2005; Rosenlund et al., 2006; Hansell et al., 2016; Dehbi et al.,

* Corresponding author. Centre for Research on Environment, Society and Health, School of GeoSciences, University of Edinburgh, Drummond Street, Edinburgh, EH89XP, UK.
E-mail address: gergo.baranyi@ed.ac.uk (G. Baranyi).

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2017; Yang et al., 2021; Yap et al., 2012).

Exposure to high levels of air pollution may be particularly detrimental and long-lasting when it intersects with sensitive periods of human development; still, few studies followed up narrow-age cohorts (Dehbi et al., 2017) which is crucial to assess the developmental timing of exposure. Evidence suggests that the time before birth and the first few years of life are critical, providing the foundation of later health and lifespan development (Baranyi et al., 2022; Darling et al., 2020). It is plausible that air pollution during this early sensitive/critical period has very long-term impact on health (and subsequent mortality), likely lasting throughout the entire life course (Steinle et al., 2020). Still, due to lack of historical air pollution data and cohort studies with life-course follow-up, previous investigations were not able to directly test this hypothesis.

Poor air quality during early life may lead to higher risk of mortality through multiple interconnected pathways. Modifications in DNA methylation patterns (Isaevska et al., 2021), altered lung (Bettiol et al., 2021) and brain development (Lubczyńska et al., 2021) are more common among young children living in polluted areas; these are key predictors of healthy life-course development and longevity (Calvin et al., 2011, 2017). For example, a systematic review of prospective cohort studies showed that one standard deviation lower cognitive test scores in youth increased mortality with 24% decades later (Calvin et al., 2011). Experiences during early childhood can have long-lasting effects on brain development and behaviour (Mackes et al., 2020). It is plausible, therefore, that air pollution in the early years damages the developing brain which leads to lower cognitive abilities in childhood and higher risk of mortality.

Using a representative cohort of the Scottish population born in 1936, we examined whether and how exposure to $PM_{2.5}$ in early life contributed to a) all-cause mortality across almost the entire life course (i.e., between age 11 and 86), to b) cause-specific mortality during late adulthood, and c) whether associations with all-cause mortality were mediated by childhood general cognitive ability. Air pollution exposure were linked to addresses at the age of 3, a period important for healthy life-course development.

2. Methods

2.1. Study population

Data were taken from the Scottish Longitudinal Study Birth Cohort of 1936 (SLSBC1936), a retrospective cohort study assembled from routinely collected administrative data, representative of the Scottish population born in 1936. SLSBC1936 is based on very high-quality data linkages between four sources, a) the 1939 National Identity Register, a census-like registry of the entire UK population carried out on the September 29, 1939 at the start of World War Two; b) the Scottish Mental Survey 1947 (SMS1947), a general cognitive ability test undertaken among almost all 11-year old Scottish schoolchildren in June 4, 1947; c) Scotland's National Health Services Central Register (NHSCR); and d) the Scottish Longitudinal Study, a 5.3% administrative sample of the Scottish population selected based on 20 semirandom birthdays and followed up since 1991 (Huang et al., 2017). In addition to the core SLSBC1936 sample, we also included individuals who would have entered the Scottish Longitudinal Study if they did not die or leave the country before in 1991; detailed information on matching procedure are available elsewhere (Huang et al., 2017). Therefore, our sample comprised individuals born in 1936 on one of the 20 Scottish Longitudinal Study birth dates, enumerated in the 1939 National Identity Register, participated in the SMS1947, and captured by the NHSCR system, totalling to a maximum sample size of 3626 individuals.

2.2. Exposure to $PM_{2.5}$ pollution

Annual level of $PM_{2.5}$ concentrations for the modelling year of 1935 was estimated using the EMEP4UK version 4.17 derived from the EMEP MSC-W version 4.17 (Simpson et al., 2012) atmospheric chemistry transport model (Vieno et al., 2010, 2014, 2016). The meteorology year used here was 2015. The meteorological driver used was the Weather Research and Forecast (WRF) model version 3.9.1.1 (Skamarock et al., 2008) based on the Global forecast system final re-analysis (GFS-FNL) as initial condition and 6-h nudging (National Centers for Environmental Prediction/National Weather Service/NOAA/U.S. Department of Commerce, 2000). Gridded anthropogenic emission of pollutants (nitrogen oxides, sulphur oxides [SO_2], ammonia [NH_3], non-methane volatile organic compounds, carbon monoxide, course [PM_{10}] and fine particulate matter [$PM_{2.5}$]) were estimated for the year 1950 (Tipping et al., 2017), and a scaled version of these data distributions, based upon activity data research, were used to make emission estimates in 1935 (Russ et al., 2021). Non-NH_3 activity data in that era are largely a reflection of the use of fossil fuels such as coal and of some oil-derived products while agricultural data, the majority source of NH_3 emissions, was derived from the Vision of Britain database (Great Britain Historical GIS Project, 2017). The model employs a horizontal resolution of $0.5 \times 0.5^{\circ}$ to a greater European domain providing the boundary condition for a nested UK domain with a horizontal resolution of $0.037 \times 0.037^{\circ}$ ($\sim$3 km $\times$ 4 km). The EMEP4UK model has been evaluated in the UK and internationally showing good agreement between modelled and observed concentrations (Lin et al., 2017; Ge et al., 2021); historical concentrations of air pollution exposure derived from this model have been used in previous epidemiological studies (Baranyi et al., 2022; Russ et al., 2021). The main source of emission in 1935 was coal and fossil fuel combustion, which led to very high spatial correlation between pollutants (Baranyi et al., 2022). As correlation coefficients between exposure to different pollutants were extremely high in our sample (Pearson's $r \sim 1$) (Table S1), we decided to present findings for $PM_{2.5}$; however, PM_{10} and SO_2 estimates for the main models were also provided. Modelled $PM_{2.5}$ concentrations ranged between 4.2 $\mu g\ m^{-3}$ to 116.9 $\mu g\ m^{-3}$ for Scotland (Fig. 1).

Participants' residential addresses were transcribed from the 1939 National Register and were geocoded using the Historical Address Geocoding – GIS software (Daras, 2015), which links historical records to contemporary addresses. Grid reference was linked to the sample using the 1939 street index (records with house numbers, street names, enumeration district and the registration district codes) and centroid of the 1939 enumeration districts, with very high linkage rate (Huang, 2023). Geocoded 1939 addresses were intersected with $PM_{2.5}$ concentrations modelled for the year 1935.

2.3. Mortality records

All-cause mortality was derived from NHSCR data indicating the month and year of death between June 1947 (i.e., date of SMS1946) and June 2022 (i.e., 901 months). The NHSCR data also includes information for those deaths occurring in other parts of the United Kingdom or overseas, which are not part of the routine Vital Event Deaths (i.e., civil registration deaths). Cause-specific mortality was obtained from the routine Vital Events Deaths database, available only for those who became part of the Scottish Longitudinal Study after 1991 and died within Scotland between April 1991 (i.e., date of 1991 Census) and December 2017 (i.e., 321 months) leading to a restricted sample. Cause of death was reported according to the International Classification of Diseases 9th Revision (ICD-9) or 10th Revision (ICD-10) which we classified into natural causes (ICD-9: 001 to 799; ICD-10: A00 to R99), cardiovascular (ICD-9: 390 to 459; ICD-10: I00 to I99), respiratory (ICD-9: 460 to 519; ICD-10: J00 to J99), and cancer-related deaths (ICD-9140 to 239; ICD-10: C00 to D48).

2.4. General cognitive ability in childhood

On the Wednesday June 4, 1947, 94% of all Scottish children born in

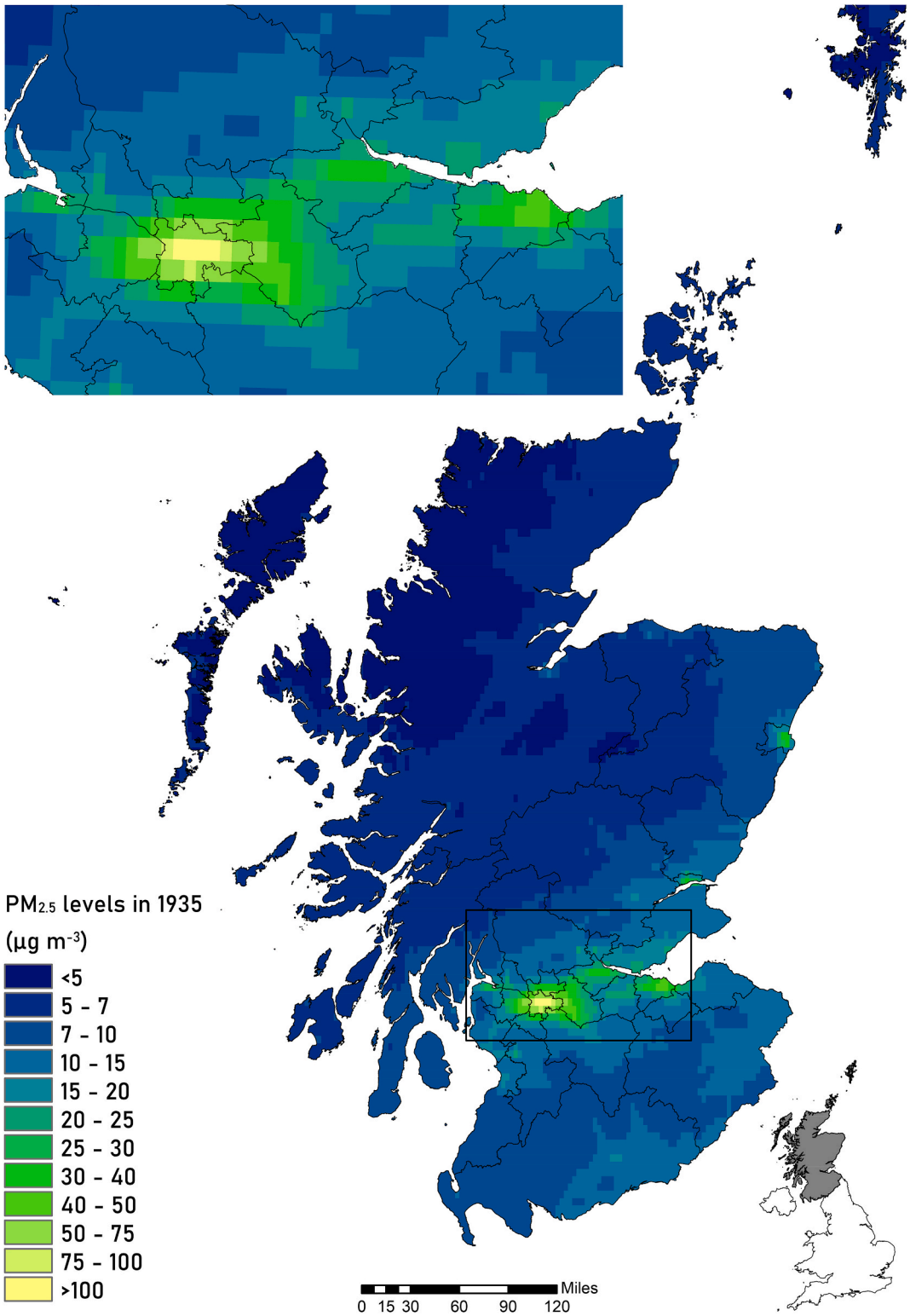

Fig. 1. Mean 1935 $PM_{2.5}$ concentration (in µg m^{-3}) in Scotland, and in the Central Belt of Scotland, estimated using the EMEP4UK atmospheric chemistry transport model with a horizontal resolution of ~3 × 4 km. Index map in the right bottom corner presents Scotland's location within the United Kingdom; black lines are council areas based on current boundaries.

1936 (n = 70805) participated on a cognitive assessment as part of the SMS1947. The survey utilised the Moray House No.12 test, a 71 item general cognitive ability test, including mental tasks such as same-opposites, word classification, analogies, reasoning, cipher decoding and spatial items (Calvin et al., 2017; Deary et al., 2004). Tests were administered in school classes across the entire country on the same day, with the same instructions and within a 45-min test interval (Calvin et al., 2017). The test score had a maximum value of 76 and it correlated highly with the Stanford-Binet test providing good criterion validity (Deary et al., 2004).

2.5. Covariates

Potential confounders of the exposure, outcome and mediator relationship were identified from the literature and are presented in a conceptual graph (Fig. 2). Sex (male, female) and age (in years) were derived from the SMS1947. Mother's age (in years), mother's marital status (married, not married) and parental occupational social position was derived from the 1939 National Identity Register. For the latter, occupational titles were first manually coded for each member of the household using the Historical International Classification of Occupations coding system (van Leeuwen et al., 2002). Occupational codes were assigned a value of occupational social position based on the HISCAM scale (Lambert et al., 2013), which is a historic measure of occupational social stratification during the 19th and early 20th centuries. The continuous HISCAM score is centred around the mean of 50 with standard deviation of 10 in the underlying population; values may range between 1 and 99 with greater numbers indicating higher social position (Lambert et al., 2013). To each participant, we assigned the father's social position (or the mother's if fathers' not available); otherwise, we calculated the average social position of all other household members.

2.6. Statistical analysis

Cox proportional hazards regressions estimated the associations between $PM_{2.5}$ and mortality using months of follow-up as the time scale. Effect estimates were presented as Hazard Ratios (HR) with 95% confidence intervals (CI) for each 10 μg m^{-3} incremental increase. Subjects were censored at the time of their death, at the time they last left Scotland (from NHSCR data), or at the end of the study if no events were registered during the follow-up period. Based on the Schoenfeld residuals, the proportional hazards assumption was met for all covariates but for sex; therefore, we incorporated strata for sex and presented stratified findings for males and females. To determine the representativeness of the analytical sample, we compared the sex distribution, average age and average Moray House test scores with the population values coming from the SMS1947 (Scottish Council for Research in Education, 1949).

The main analysis focussed on early life $PM_{2.5}$ exposure and all-cause mortality. Two confounder models were set *a priori*: Model 1 controlled for age and sex (strata); Model 2 further adjusted for parental occupational position, mother's age, and mother's marital status. In addition to treating the associations as time-independent, we also tested whether the relationship between $PM_{2.5}$ exposure and all-cause mortality changed during follow-up by splitting the follow-up time into four intervals: first 527 months (i.e., average age of 11–55 years), from 528 to 647 months (i.e., average age of 55–65 years), from 648 to 767 months (i.e., average age of 65–75 years), and from 768 to 901 months (i.e., average age of 75–86 years). Finally, based on Model 2 adjustments we explored concentration-response relationship by adding penalized splines with 2, 3 and 4 degrees of freedom. The best model was determined based on the Bayesian Information Criterion (BIC) and linearity of relationship was examined with χ^2 test.

Associations between $PM_{2.5}$ in early life and mortality due to natural causes, as well as cardiovascular, respiratory and cancer mortality were estimated in competing risks analysis. Models were operationalised in Cox proportional hazards regression by fitting two endpoints at the same time (i.e., outcome of interest versus other deaths) with distinct baseline hazards for $PM_{2.5}$, age, and sex (strata), and shared coefficients for parental occupational social position, mother's age, and mother's marital status. In contrary to calculating cause-specific hazards regression, this approach takes into consideration that competing events are mutually exclusive (Therneau et al., 2022). Model 1 and Model 2 adjustments, as well as sex-stratified findings were presented.

Total association between $PM_{2.5}$ exposure and all-cause mortality was decomposed into natural direct and natural indirect (through childhood general cognitive ability) effects applying regression-based causal mediation analysis within the counterfactual framework (VanderWeele and Vansteelandt, 2009). For the mediator model, we fitted a linear regression, for the outcome model a Cox regression; the same Model 2 confounders were included in both mediator and outcome models. Percentage mediated was expressed as the percentage of total association explained by the mediator; 95% CIs for total, natural direct and natural indirect effects were estimated based on 10000 bootstrap

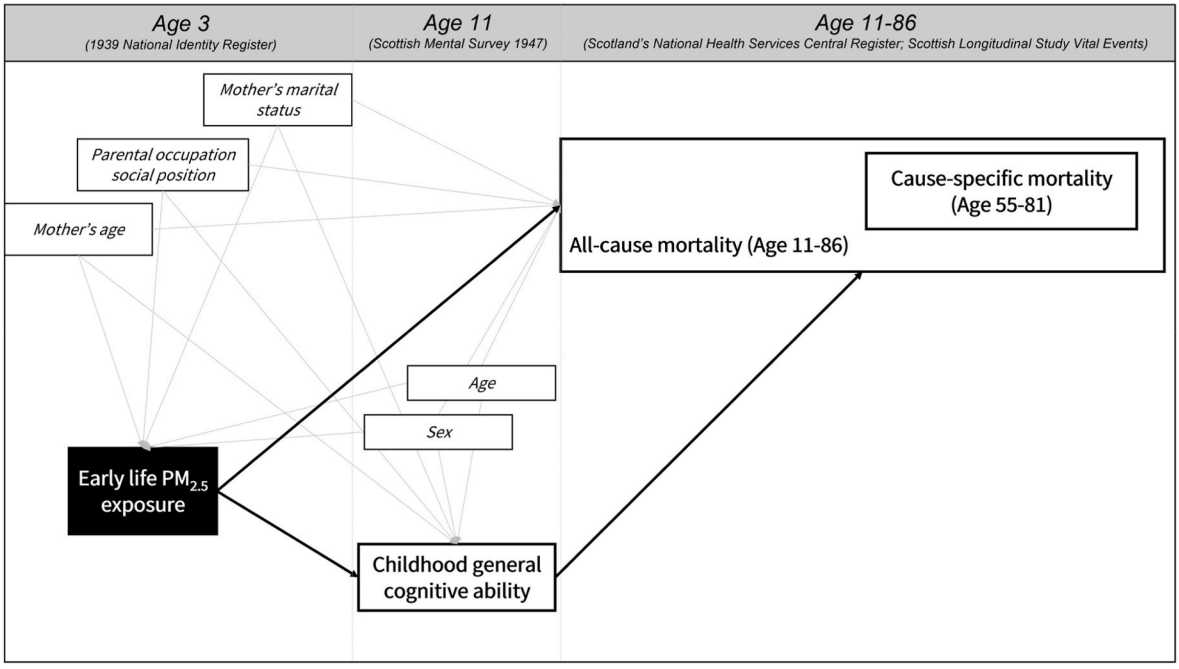

Fig. 2. Conceptual graph presenting associations between exposure, mediator, outcome and confounders, and the main source of data. Associations between confounders are not shown for simplicity, solid black lines are associations of interest. Geocoded 1939 addresses were linked to $PM_{2.5}$ concentrations estimated with the EMEP4UK model for the year 1935.

replications. To contrast levels of exposure, $PM_{2.5}$ exposure was dichotomised as <50 versus ≥50 μg m^{-3}, a cut off separating the highest ~20% from the rest of the sample. We presented findings for the non-stratified sample only.

Six sets of sensitivity analyses were carried out. First, we presented main results (i.e., all-cause mortality) for alternative exposure operationalisations (i.e., interquartile range [IQR] increase, threshold [<50, ≥50 μg m^{-3}]). Second, proportion of missing data was significant for some of the covariates, therefore, we reran main models with multiple imputation by chained equation. Number of imputations was determined automatically based on the proportion of incomplete cases (Nahhas, 2023). Third, we dropped individuals with extremely high $PM_{2.5}$ values (≥100 μg m^{-3}) residing in the centre of Glasgow City and reran main models. Fourth, instead of fitting two endpoints in Cox regression, competing risks were calculated with the Fine-Gray proportional subdistribution hazards regression. Fifth, we presented the mediation analysis with an alternative cut-off for 'low' and 'high' air pollution levels (<40 versus ≥40 μg m^{-3}) capturing ~75% versus ~25% of the sample. Last, we provided all models after adjusting for urban versus rural area of residence, which was determined based on living in Aberdeen, Dundee, Edinburgh, or Glasgow (i.e., urban) versus in other areas (i.e., rural), by intersecting 1939 addresses with current council boundaries.

Analyses were carried out using the *survival* (Therneau, 2023), *regmedint* (Yoshida et al., 2022), *mice* (van Buuren and Groothuis-Oudshoorn, 2011) and *tidycmprsk* (Sjoberg and Fei, 2022) packages in R 4.2.2 (R Core Team. R, 2022).

3. Results

The final SLSBC1936 sample without missing data included 2734 individuals (48.4% females) contributing to a total of 1,833,517 person-months (152,793.1 person-years) at risk with a median follow-up time of 771 months (64.3 years). During follow-up, 1608 individuals died, 475 left the study and 651 were still alive at the end of the study. The average exposure to $PM_{2.5}$ was 31.3 μg m^{-3} (SD = 32.6; IQR = 9.3–39.0). Comparing the SLSBC1936 analytical sample with the population of individuals born in 1936 (i.e., the main SMS1947 sample) suggested no difference across sex, age, and childhood cognitive ability (Table 1).

After adjusting for age and sex (strata), we found 3% higher hazard of all-cause mortality per 10 μg m^{-3} increment increase in early life $PM_{2.5}$ exposure (HR = 1.03, 95% CI: 1.01–1.04). The association remained the same after further adjustments for parental occupation social position, mother's marital status, and mother's age (HR = 1.03, 95% CI: 1.01–1.04) (Table 2). Associations were varying across the life course: while between age 11 and 65 there was no association, 10 μg m^{-3} higher early life $PM_{2.5}$ exposure increased the hazard of all-cause mortality between age 65 and 75 years by 4% (95% CI: 1.02–1.07), and between age 75 and 86 by 3% (95% CI: 1.00–1.05) (Model 2). Stratified analyses suggested that among females the association was strongest between age 75–86, while among males it was strongest between age 65–75 (Table 2). Model estimates for PM_{10} and SO_2 are presented in Table S2. Furthermore, in the total sample, concentration-response relationship was monotonic, linear and best-fitting with two degrees of freedom (likelihood ratio test for non-linear component: $\chi^2 = 0.43$; $p = 0.530$; see Bayesian Information Criterion values in Table S3). HRs constantly increased with increasing $PM_{2.5}$ concentrations but first crossed the value of HR = 1.0 at the value of ~38 μg m^{-3}. Although the shape of the association visually differed between females and males, confidence intervals were wide and overlapping (Fig. 3).

The association with cause-specific mortality was assessed in a restricted sample ($n = 1947$) as information on cause of death was only available between April 1991 and December 2017 for those died in Scotland. During this period 956 deaths were registered: 939 due to natural causes including 321 cardiovascular, 109 respiratory, and 341 cancer-related deaths. Competing risks analysis with adjustment for all covariates suggested that early life $PM_{2.5}$ exposure increased the hazard of cancer-related mortality by 5% (95% CI: 1.02–1.08) but there was no association with cardiovascular (HR = 1.00, 95% CI: 0.97–1.04) or

Table 1
Characteristics of participants in the analytical sample and in the respective population.

Characteristics	Data source	Analytical sample (SLSBC1936) (n = 2734)	Population (SMS1947) (n = 70805)[a]
$PM_{2.5}$ exposure in early life in μg m^{-3}, mean ± SD	Age 3 (1939NIR, September 28, 1939)	31.3 ± 32.6	NA
Parental occupational social position, mean ± SD		53.8 ± 9.4	
Mother's marital status, n (%)			
Married		2645 (96.7%)	
Not married		89 (3.3%)	
Mother's age in years, mean ± SD		32.1 ± 6.4	
Age in years at the Moray House test, mean ± SD	Age 11 (SMS1947, June 4, 1947)	11.0 ± 0.3	10.9 ± 0.3[b]
Sex, n (%)			
Female		1322 (48.4%)	34996 (49.4%)
Male		1412 (51.6%)	35809 (50.6%)
Moray House test score, mean ± SD		36.8 ± 15.5	36.7 ± 16.1

Source: Scottish Longitudinal Study. Abbreviation: NA = not applicable; SD = standard deviation; SLSBC1936=Scottish Longitudinal Study Birth Cohort of 1936; SMS1947=Scottish Mental Survey 1947; 1939NIR = 1939 National Identity Register.

[a] Reference values are from (Scottish Council for Research in Education, 1949).

[b] Own calculation based on Table IV (page 82 (Scottish Council for Research in Education, 1949)).

Table 2
Associations between early life $PM_{2.5}$ exposure and all-cause mortality in the Scottish Longitudinal Study Birth Cohort of 1936 a) during the total follow up and b) by follow-up intervals.

Covariates	Model 1[a] HR (95% CI)	Model 2[b]		
		Total HR (95% CI)	Female HR (95% CI)	Male HR (95% CI)
a) During total follow-up				
$PM_{2.5}$ in early life (10 μg m^{-3} increase)	**1.03 (1.01–1.04)**	**1.03 (1.01–1.04)**	**1.03 (1.01–1.05)**	**1.02 (1.00–1.04)**
b) By follow-up intervals				
$PM_{2.5}$ in early life (10 μg m^{-3} increase)				
Age 11–55 year	1.01 (0.97–1.05)	1.00 (0.96–1.04)	1.01 (0.94–1.08)	1.00 (0.95–1.05)
Age 55–65 year	1.01 (0.97–1.05)	1.01 (0.97–1.05)	1.05 (0.99–1.12)	0.99 (0.94–1.03)
Age 65–75 year	**1.05 (1.02–1.08)**	**1.04 (1.02–1.07)**	1.02 (0.97–1.06)	**1.06 (1.03–1.10)**
Age 75–86 year	**1.03 (1.00–1.05)**	**1.03 (1.00–1.05)**	**1.04 (1.01–1.07)**	1.02 (0.98–1.05)

Source: Scottish Longitudinal Study. The sample size was $n = 2734$. Cox proportional hazard regression were fitted and Hazard Ratios (HR) with 95% confidence intervals (CI) are presented. In the total sample, sex as strata was included. Bolded values are significant ($p < 0.05$). All-cause mortality was available between June 1947 and June 2022 from Scotland's National Health Services Central Register. Abbreviation: SD = standard deviation.

[a] Model 1 was adjusted for age and sex (strata).

[b] Model 2 was adjusted for age, (sex (strata)) parental occupational social position, mother's marital status, and mother's age.

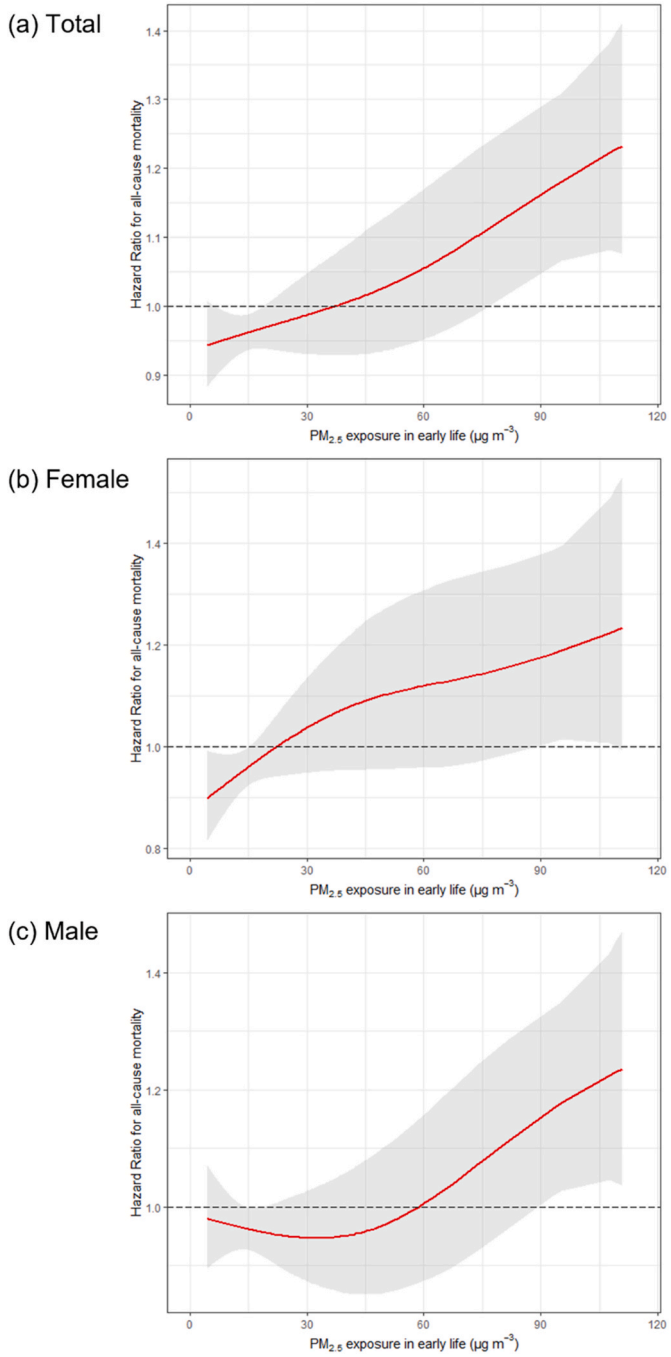

Fig. 3. Concentration-response relationship between $PM_{2.5}$ in early life and all-cause mortality in the Scottish Longitudinal Study Birth Cohort of 1936 for the (a) total sample; and among (b) females and (c) males. Curves were obtained by penalized splines with two degrees of freedom; observed relationships were linear. All-cause mortality was extracted from Scotland's National Health Services Central Register available between June 1947 and June 2022. Model was adjusted for age, (sex (strata)) parental occupational social position, mother's marital status, and mother's age. The total sample size was $n = 2734$. Source: Scottish Longitudinal Study.

respiratory mortality (HR = 1.02, 95% CI: 0.96–1.07) (Table 3). Sex-specific analyses showed that the association with cancer-related mortality was prominent in the female subsample. As a *post-hoc* analysis, we further explored whether lung cancer (ICD-9: 162; ICD-10: C34) was the main driver of cancer-related mortality among females, which was confirmed (HR = 1.11, 95% CI: 1.02–1.21). Among males, mortality due to natural cases other than cancer, cardiovascular or respiratory was

Table 3
Associations between early life $PM_{2.5}$ exposure and cause-specific mortality in the Scottish Longitudinal Study Birth Cohort of 1936.

Cause-specific mortality	Model 1[a] HR (95% CI)	Model 2[b]		
		Total HR (95% CI)	Female HR (95% CI)	Male HR (95% CI)
$PM_{2.5}$ in early life (10 μg m^{-3} increase)				
All causes	**1.03 (1.01–1.05)**	**1.03 (1.01–1.05)**	1.02 (0.99–1.05)	**1.04 (1.01–1.06)**
All natural causes	**1.03 (1.01–1.05)**	**1.03 (1.01–1.05)**	1.03 (1.00–1.06)	**1.04 (1.01–1.06)**
Cancer	**1.05 (1.02–1.08)**	**1.05 (1.02–1.08)**	**1.08 (1.03–1.13)**	1.03 (0.99–1.07)
Cardiovascular	1.00 (0.97–1.04)	1.00 (0.97–1.04)	0.98 (0.93–1.04)	1.01 (0.97–1.06)
Respiratory	1.02 (0.96–1.08)	1.02 (0.96–1.07)	1.02 (0.94–1.10)	1.02 (0.94–1.11)
Other causes	**1.06 (1.01–1.10)**	**1.05 (1.01–1.10)**	0.99 (0.91–1.08)	**1.08 (1.03–1.14)**

Source: Scottish Longitudinal Study. The total sample size was $n = 1947$. Cox proportional hazard regressions were run with competing risks (i.e., outcome of interest versus other mortality) for each outcome separately. Hazard Ratios (HR) with 95% confidence intervals (CI) are presented. Bolded values are significant ($p < 0.05$). Cause-specific mortality was extracted from the Vital Events Deaths database, available for those who died between April 1991 and December 2017 in Scotland.

[a] Model 1 was adjusted for age and sex(strata).

[b] Model 2 was adjusted for age, (sex [strata]) parental occupational social position, mother's marital status, and mother's age.

significantly associated with early life exposure to $PM_{2.5}$. Although not statistically significant, *post-hoc* we found increased risk of death (HR = 1.08, 95% CI: 1.00–1.17; $p = 0.055$) due to neurodegenerative disorders (Alzheimer's disease and related disorders [ICD-9: 046.1, 290.0–290.4, 294, 331; ICD-10: F00–F03, G30-31], Parkinson's disease [ICD-9: 332; ICD-10: G20-22], amyotrophic lateral sclerosis [ICD-9: 335.2; ICD-10: G12.2]).

The total effect of early life $PM_{2.5}$ exposure on all-cause mortality was decomposed into natural direct and natural indirect effects mediated by childhood general cognitive ability. Individuals with 'high' early life $PM_{2.5}$ exposure (≥50 μg m^{-3}) had a 39-month shorter median survival time in comparison to those from relatively 'low' concentration areas (<50 μg m^{-3}). Regression-based causal mediation analysis suggested that – in the fully adjusted model – being exposed to high concentrations of $PM_{2.5}$ was associated with a 22% higher risk of all-cause mortality (95% CI: 1.08–1.38) (i.e., *total effects*). Approximately 25% of the total effects was mediated by general cognitive ability (HR = 1.05; 95% CI: 1.03–1.07) (i.e., *natural indirect effects*): higher $PM_{2.5}$ levels contributed to lower test scores, and lower test scores were associated with higher risk of all-cause mortality. The *natural direct effect* (i.e., not explained by general cognitive ability) of $PM_{2.5}$ exposure on all-cause mortality was HR = 1.17 (95% CI: 1.03–1.32) (Fig. 4; Table S4).

Sensitivity analyses determined that 1-IQR increase in $PM_{2.5}$ exposure was associated with 8% (95% CI: 1.03–1.13) increased risk of all-cause mortality in the fully adjusted model (Table S5); findings for dichotomised air pollution levels (<50 μg m^{-3}, ≥50 μg m^{-3}) can be found in Table S6. Imputing missing data through multiple imputation did not change the results (Table S7); excluding participants with very high exposure (≥100 μg m^{-3}) only led to marginal changes (Table S8). Exploring competing risks with Fine-Gray proportional subdistribution hazards regression produced the same cause-specific associations as presented earlier (Table S9). After applying the 40 μg m^{-3} cut-off for the mediation analysis, 21% of the total association was mediated by childhood cognitive ability (Fig. S1). Finally, adjusting for urban-rural differences in 1939 slightly attenuated findings for all-cause mortality (i.e., associations did not remain significant for females) (Table S10), but did not change the pattern of cause-specific associations (Table S11). In the total sample, regression-based mediation analysis did not converge

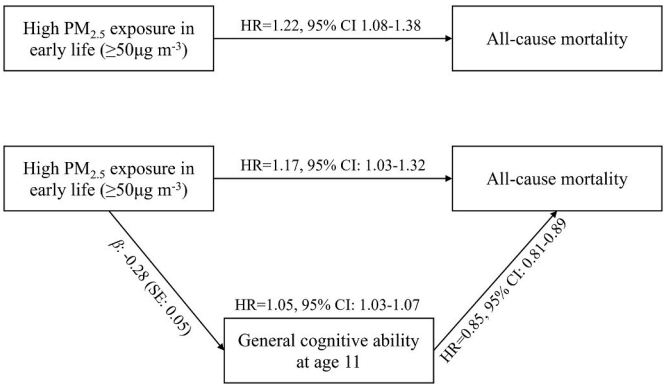

Fig. 4. Total, natural direct, and natural indirect effects between 'high' early life $PM_{2.5}$ exposure (≥50 μg m^{-3}) and all-cause mortality, with mediation through childhood general cognitive ability. All-cause mortality was available between June 1947 and June 2022 from Scotland's National Health Services Central Register. Total, natural direct, and natural indirect effects were estimated with regression-based causal mediation analysis, their 95% CIs with 10000 bootstrap replications. Models were adjusted for age, sex, parental occupational social position, mother's marital status, and mother's age. The total sample size was $n = 2734$. Source: Scottish Longitudinal Study.

after adjusting for residential location; however, among males 17% of the total association was still mediated by childhood cognitive ability (Fig. S2).

4. Discussion

Using a representative administrative cohort, we explored the associations between $PM_{2.5}$ concentrations in early life and mortality across 75 years in 2734 participants. Exposure to higher levels of $PM_{2.5}$ were associated with increased hazard of all-cause mortality, especially between the ages of 65 and 86. Competing risk analyses on a restricted sample highlighted that associations were only present for cancer-related deaths, especially for lung-cancer mortality among females. One potential pathway connecting early life air pollution exposure to mortality is via lower childhood cognitive ability, which mediated 25% of the total associations in our sample.

This study strengthens the evidence base linking long-term $PM_{2.5}$ exposure to increased risk of mortality in the UK and worldwide (Chen and Hoek, 2020; Filleul et al., 2005; Rosenlund et al., 2006; Hansell et al., 2016; Dehbi et al., 2017; Yang et al., 2021; Yap et al., 2012). The estimated HR was 1.03 per 10 μg m^{-3} incremental increase for all-cause mortality, which is much lower than the risk (Risk Ratio[RR] = 1.08) estimated in a recent meta-analysis (Chen and Hoek, 2020); however, this is not unexpected as previous findings with long-term follow-ups pointed towards decreasing effect sizes by more distal air pollution exposures in comparison to proximal ones (Hansell et al., 2016; Elliott et al., 2007). Given the wide range of $PM_{2.5}$ exposures, and the gentle, but steadily increasing slope of association, $PM_{2.5}$ first crossed the HR = 1 at the relatively higher concentration of 38 μg m^{-3}, which is much higher than thresholds of unhealthy exposure suggested by the literature (Chen and Hoek, 2020; Strak et al., 2021), including the WHO guidelines (World Health Organization, 2021). We are not aware of previous investigations with a follow-up time of longer than 40 years (e.g. (Hansell et al., 2016),) and making direct comparison to the literature is challenging; still, it is remarkable that toxic levels of air pollution might contribute to mortality 60–80 years after exposure.

Early life $PM_{2.5}$ exposure was more strongly associated with all-cause mortality between age 65 and 86 and with cancer-related mortality, especially lung cancer. In contrary to all-cause mortality, HR for lung cancer in our female subsample (HR = 1.11) was close to identical to risks reported in the literature based on shorter follow-up studies (RR = 1.12) (Chen and Hoek, 2020). Cancer-related mortality is the second leading cause of death according to the Global Burden of Disease Study, with tracheal, bronchus, and lung cancer being the leading cause of cancer deaths (Fitzmaurice et al., 2017). Their relative proportion in comparison to other cancers is particularly high between the ages of 60 and 80 years (Fitzmaurice et al., 2017), which overlaps with our findings. In contrary to the literature suggesting consistent associations between $PM_{2.5}$ pollution and cardiovascular mortality (Chen and Hoek, 2020), there was null association in our study. It might be plausible that $PM_{2.5}$ in early life, or its chemical composition in the late 1930s, did not have such a long-lasting association with cardiovascular diseases or that early life is not a sensitive period for late adulthood cardiovascular events. Air pollution exposure has been also associated with neurodegenerative disorders in the literature (Shi et al., 2020), with stronger associations in males (Cole-Hunter et al., 2023), which align with our preliminary findings. Still, these hypotheses need to be explored in further investigations.

In early life, inhaled air pollutants can directly affect healthy development in children (Isaevska et al., 2021; Bettiol et al., 2021). Lung growth has been shown to be reduced among children exposed to higher air pollution levels (Gauderman et al., 2004) and they have also higher risks of developing asthma (Bettiol et al., 2021). Toxic environmental exposures – through oxidative stress and inflammation – are also associated with molecular changes in the somatic cells, and these alterations might survive subsequent cell replications and affect healthy development and longevity. For example, modified DNA methylation patterns, responsible for gene expression and genome stability, as well as shorter telomeres, a marker of cellular ageing, have been associated with air pollution exposure in early and later life (Isaevska et al., 2021; Miri et al., 2019). A recent Scottish study, based on a sample (Lothian Birth Cohort 1936) selected from the same 1936-born population as in our study, showed that higher air pollution exposure around birth was associated with shorter DNA methylation-based telomere length in late adulthood, especially among females (Baranyi et al., 2022), even after adjusting for a variety of life-course social and behavioural (e.g. smoking) risk factors. Epigenetic markers increase the risk of developing cancer (Kulis et al., 2010) and mortality (Marioni et al., 2015), presenting a plausible explanation for our sex-specific findings related to cancer mortality.

Air pollution in early life may also affect brain development: maternal air pollution exposure from the 25th gestational week onwards is associated with head growth (Clemens et al., 2017) but being exposed postnatal $PM_{2.5}$ concentration is also linked to poorer cognitive performance in childhood (Ni et al., 2022; Chiu et al., 2016; Lopuszanska and Samardakiewicz, 2020). The human brain undergoes rapid developments in the early years which continues well into childhood with the differentiation and maturation of neurons and myelination of axons (Hedman et al., 2012; Stiles and Jernigan, 2010). A whole population follow up on the SMS1947 with more than 65000 participants showed that higher general cognitive ability scores in childhood decreased all-cause mortality and cause-specific mortality for almost all major causes of death, including smoking-related cancers and dementia (Calvin et al., 2017). Higher cognitive ability in childhood is a powerful predictor of longevity with pathways including higher educational attainment and adult socioeconomic status, which can impact among others health literacy, health behaviour, and diseases management (Calvin et al., 2011; Sörberg Wallin et al., 2018). Our findings add that higher early life $PM_{2.5}$ exposure modestly decreases general cognitive ability in childhood (even after adjusting for parental occupational social position), thus indirectly contributing to all-cause mortality; approximately one-quarter of the total association was mediated through childhood cognitive ability presenting an important pathway between early life toxic exposure and mortality.

This study demonstrated the feasibility of exploring the relationship between early life $PM_{2.5}$ exposure and mortality over almost the entire life course. The study benefitted from high quality data linkages between different historical and contemporary administrative sources,

included key family and household confounders in early childhood, a validated measure of general cognitive ability at age 11, and an exceptionally long follow-up of mortality records stretching over 75 years. Residential information at age 3 was derived from administrative data, thus not prone to recall bias. However, several key limitations should be considered when interpreting the results. First, cause-specific mortality was only available for a relatively shorter follow-up time (~26 years). Although we do not assume that longer follow-up would have change the reported associations with cancer-related deaths, it is plausible that adding further mortality records across the life course may reveal other cause-specific mortality associations in future studies. Second, information on mortality before age 11 was not available in the SLSBC1936. Given the high mortality rates among 1-year olds in England during the 1930s (Birth- and Death-Rates for 1936 in England, 1937), and the strong association between $PM_{2.5}$ concentrations and infant mortality in high pollution contexts (e.g. India (deSouza et al., 2022)), it is plausible that air pollution had a strong effect on mortality in the earlier years which we were not able to capture. Third, early life residential location was only available in the 1939 National Identity Register. As the probability of residential mobility for this birth cohort was relatively low in their earliest years (Falkingham et al., 2016), we cannot ascertain that air pollution exposure only during postnatal periods contributed to higher risk of mortality (as opposed to prenatal). Moreover, missing residential history during childhood introduces further uncertainty to identify sensitive (or critical) exposure windows. Fourth, making valid causal inference on natural direct and indirect effects requires a set of key assumptions: i) no unmeasured treatment-outcome confounding; ii) no unmeasured mediator-outcome confounding; iii) no unmeasured treatment-mediator confounding; iv) no mediator-outcome confounder affected by the treatment (Vanderweele, 2015). As the availability of administrative data strongly determined the variables we were able to include (e.g., no data on maternal smoking, childhood health), unmeasured confounding might have led to bias in estimating natural direct and indirect effects. Fifth, there are inherent uncertainties at all stages of the emissions estimation process, even for the present day, and many of these problems are magnified when trying to recreate a historical context (e.g., emission quantification). The same atmospheric chemistry transport models for newer modelling years (2009–2010) have been evaluated against concurrent $PM_{2.5}$ concentrations, which indicated good agreement between estimated and measured concentrations, but also suggested that $PM_{2.5}$ concentrations might be underestimated in the EMEP4UK models (Lin et al., 2017). While there are increasing uncertainties when pollutants are estimated further back in time, their relative spatial concentrations can be considered as sufficiently accurate. Further efforts to quantify historical emissions are warranted to produce more reliable estimates. We presented main findings for $PM_{2.5}$ but given very high correlation with other pollutants (e.g., PM_{10}, SO_2) it is impossible to disentangle separate effects in historical contexts. Last, key air pollution regulatory policies throughout the 20th century (e.g., Clean Air Acts 1956, 1968, 1993) reduced $PM_{2.5}$ concentrations in the UK (Carnell et al., 2019), and probably changed its chemical components. Pollutant concentrations experienced by sample participants in their early lives are rarely present in high-income countries anymore. Still, with increasing global inequities in pollution though raising concentration in low- and middle-income countries (World Health Organization, 2021), our findings have relevant global implications.

Future studies could capitalise on routinely collected data utilising census responses, healthcare service use data and Vital Events on marriages and children's birth to extract information on residential locations across the entire life course and provide a more comprehensive assessment on how air pollution contributes to morbidity and mortality from foetal period onwards. Further high-quality measures of historical area-level context are required (e.g., area deprivation, population density), to disentangle the very long-term impact of environmental exposures on health and to lower the risk of unaddressed confounding. Mechanistic pathways, including social, cognitive, and biological processes, should be investigated which have the potential to connect childhood exposure to late adulthood health.

5. Conclusions

Exposure to higher $PM_{2.5}$ in early life was associated with higher all-cause and cancer-related mortality, especially between the ages of 65 and 75, with one-quarter of the association being mediated through lower childhood general cognitive ability. Future investigation should explore mechanistic pathways and assess the relative importance of air pollution exposure at different time-points in our lives. The findings suggest that air pollution may have very long-term impact on health and longevity, with its detrimental impact lasting long after mitigation policies reduced concentration levels.

Credit author statement

Gergo Baranyi: conceptualization, formal analysis, methodology, writing-original draft. **Lee Williamson**: conceptualization, data curation, writing-review & editing. **Zhiqiang Feng**: conceptualization, data curation, writing-review & editing. **Sam Tomlinson**: software, resources, writing-review & editing. **Massimo Vieno**: software, resources, writing-review & editing. **Chris Dibben**: conceptualization, methodology, writing-review & editing, supervision, funding acquisition.

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Ethics approval

This study was approved by the Research Ethics and Integrity Committee Secretary (2019-332) at the University of Edinburgh, School of Geosciences.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117021.

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