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Confounding mechanisms and adjustment strategies in air pollution epidemiology: a case study assessment with the UK Biobank cohort

Jacopo Vanoli[1,2,*], Lina Madaniyazi[1], Massimo Stafoggia[3], Chris Fook Sheng Ng[4], Antonio Gasparrini[2]

[1]School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[2]Environment & Health Modelling (EHM) Lab, Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, United Kingdom
[3]Department of Epidemiology, Lazio Region Health Service ASL ROMA 1, Rome, Italy
[4]Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

*Corresponding author. Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, United Kingdom. E-mail: jacopo.vanoli@alumni.lshtm.ac.uk.

Abstract

Background: Cohort studies are instrumental in examining long-term risks associated with environmental exposures but require appropriate control for various confounding effects. In this contribution, we assessed this issue by investigating the relationship between fine particulate matter ($PM_{2.5}$) exposure and mortality in a UK-based cohort.

Methods: We analysed data from half a million adults in the UK Biobank linked with time-varying individual-level exposure data and followed up during the period 2006–21. The assessment focused on confounding related to spatial and temporal patterns as well as due to measurable variables, including both contextual and individual-level factors. We performed an evaluation consisting of descriptive analyses, specification and interpretation of direct acyclic graphs (DAGs), and comparison of results from survival models.

Results: We found correlations between $PM_{2.5}$ exposure and mortality rates across time, geographical areas, and categories of measurable variables. The DAG indicated complex causal pathways and the need to adjust for a wide set of potential confounders. The regression analysis confirmed these patterns: the fully adjusted model estimated a hazard ratio (HR) of 1.25 (95% CI: 1.06–1.49) per 10 $\mu g/m^3$ increments in $PM_{2.5}$, but the association reversed to 0.82 (0.76–0.87) when excluding control for recruitment centre, suggesting strong spatial confounding. Calendar time showed stronger confounding effects compared to age. Area-level socio-economic indicators were more important than individual-level counterparts, while lack of control for lifestyle factors led to a noticeable overestimation.

Conclusions: This case-study illustration elucidates various confounding mechanisms in cohort studies on environmental risks and offers a critical evaluation of alternative adjustment strategies.

Keywords: UK Biobank; air pollution; confounding; cohort study; long-term.

Key Messages

- The assessment of long-term risks associated with environmental exposures such as air pollution relies on observational analyses of cohort datasets that are prone to various confounding mechanisms.
- This study offers a comprehensive overview based on theoretical considerations and empirical findings, using as a case study an analysis of the UK Biobank cohort.
- The analysis of direct acyclic graphs (DAGs) and substantive results suggest various potential confounding mechanisms, particularly those related to unmeasured spatial differences in exposure levels and baseline risks, as well as individual-level lifestyle factors.

Introduction

Epidemiological evidence on long-term risks of environmental stressors, such as air pollution, comes mostly from population-based cohort studies [1, 2]. Such observational studies require specific design choices and covariate adjustment to avoid confounding due to differential exposure and health risks across individuals, as well as over space and time [3–5].

In this article, we discussed different confounding processes that can affect cohort studies on environmental risk factors, differentiating them based on their source. Specifically, we classified them into spatial and temporal mechanisms, as well as those related to measurable risk factors, the latter distinguished between contextual and individual-level variables. In this case, spatial confounding implies that the comparison of subjects living in different

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areas is prone to confounding due to differential baseline risks related to environmental exposures [4]. Similarly, temporal confounding can manifest itself through collinear patterns of exposure and outcome across time [6]. Lastly, confounding can be related to measurable variables, including a wide spectrum of risk factors such as socio-economic indices, environmental conditions, as well as lifestyle and other personal characteristics.

Control for residual spatial and temporal confounding is usually achieved by implementing specific design and modelling strategies, such as stratification [4, 7]. Differently, confounding patterns related to putative risk factors are more difficult to conceptualize and untangle. Their control can be achieved by the inclusion of measurable variables in regression models, and decisions about their selection usually require additional assumptions on the potential causal pathways, facilitated by the application of specific methods such as directed acyclic graphs (DAGs) [8]. Previous works have discussed methodological and practical issues related to confounding in cohort studies on air pollution [4, 9, 10]. However, several questions remain unaddressed, such as the appropriate strategies to account for spatial and temporal differences in time-to-event analysis, or the role of individual-level factors, particularly those related to lifestyle aspects that are rarely available in large administrative health databases.

In this contribution, we aimed to elucidate and assess potential confounding mechanisms in studies on long-term exposures to environmental stressors, using as a case study a published analysis on air pollution and mortality in the UK Biobank (UKB) [11]. Through theoretical considerations, descriptive analyses, and empirical estimates of health risk associations, we discussed various confounding processes and model adjustment strategies.

Data and methods

UK Biobank

The UKB is a large biomedical database that includes approximately half a million participants [12]. Recruitment occurred between 2006 and 2010 for adults aged 40–69 residing within 10 miles of one of 22 assessment centres spread across the UK. The catchment areas of the assessment centres were chosen based on sufficient proximity to highly populated regions. The participants underwent a first in-person visit during which they completed several questionnaires regarding their personal characteristics, lifestyles, and medical history. Specific details regarding the UKB database can be found on the showcase website (https://biobank.ndph.ox.ac.uk/showcase/).

Air pollution exposure

Individual-level exposure to outdoor fine particulate matter ($PM_{2.5}$) was assigned to each participant accounting for their residential history across the follow-up. The original $PM_{2.5}$ data were defined at daily level and predicted on a 1-km grid across the UK in the period 2003–21 using a hybrid spatio-temporal machine learning model [13]. The residential data were available in the UKB database, including periods and geocoded locations with 100 m rounding. The linkage process has been described in a previous publication [14].

Outcomes

At the time of enrolment, the participants consented to access their electronic health records. Cause and date of death were extracted from the national death registries. The outcome events were defined as deaths due to non-accidental causes (ICD10: A00-R99).

Selection of confounders

We selected the set of confounders based on substantive knowledge of their role in the relationship between outdoor $PM_{2.5}$ concentrations (as a proxy for individual exposure) and mortality, and theoretical results from the application of DAGs. Contextual features were represented by the assessment centre (as a proxy for residential location) and variables defined at the residence at recruitment time, including area-level deprivation measured by the Townsend deprivation index (TDI), the percentage of greenspace within a 1000 m buffer, and urban–rural classification. Individual-level confounders were separated into socio-economic factors (ethnic background, education level, household income, and employment status) and physical and lifestyle characteristics (smoking status and intensity, alcohol intake, waist-to-hip ratio, physical activity, and living alone). All of them were defined at baseline. Details on the covariate definitions and their correlation are provided in the supplementary file (Supplementary Fig. S1 and Table S1).

The assumptions on the causal paths assumed between outdoor $PM_{2.5}$ exposure, the other risk factors listed above, and mortality are represented as a DAG of Fig. 1. In this study, we considered confounders as variables included in a minimally sufficient adjustment set identified through a DAG, which theoretically ensures adequate control of confounding bias.

Statistical analysis

The analysis was based on a design strategy and model selection described in detail in previous work [11]. We applied a Cox proportional hazard model with time-varying exposures. The exposure index was defined at individual level as the time-varying average of $PM_{2.5}$ in the eight calendar years before the event. We assumed a linear exposure-response relationship between exposure and outcome. The end of follow-up was determined either by subject's death, loss to follow-up, or the administrative end of mortality linkage (31 December 2022), extending the follow-up of the previous analysis [11].

In our main (full) model, we used calendar time as the time axis, we stratified by indicators of sex, assessment centre, and year of birth, and finally, we adjusted directly for all the other covariates listed in the previous section. We then defined alternative adjustment strategies to examine potential confounding mechanisms, specifically by excluding confounders or stratifying variables from the model (individually or in groups), and by varying time axes and control of trends.

We conducted a sensitivity analysis for the inclusion of the assessment centre in the statistical model using different specifications, following a previous work [10]. Specifically, we used dummy variables or random effects with a gamma distribution or normal distribution.

Estimates of the associations were reported as hazard ratios (HRs) for non-accidental mortality per 10 $\mu g/m^3$ increments in $PM_{2.5}$, with 95% confidence intervals (CIs). Missing values in the baseline covariates were imputed using multiple imputations by chained equation (MICE). For simplicity, we used the results of a single imputation.

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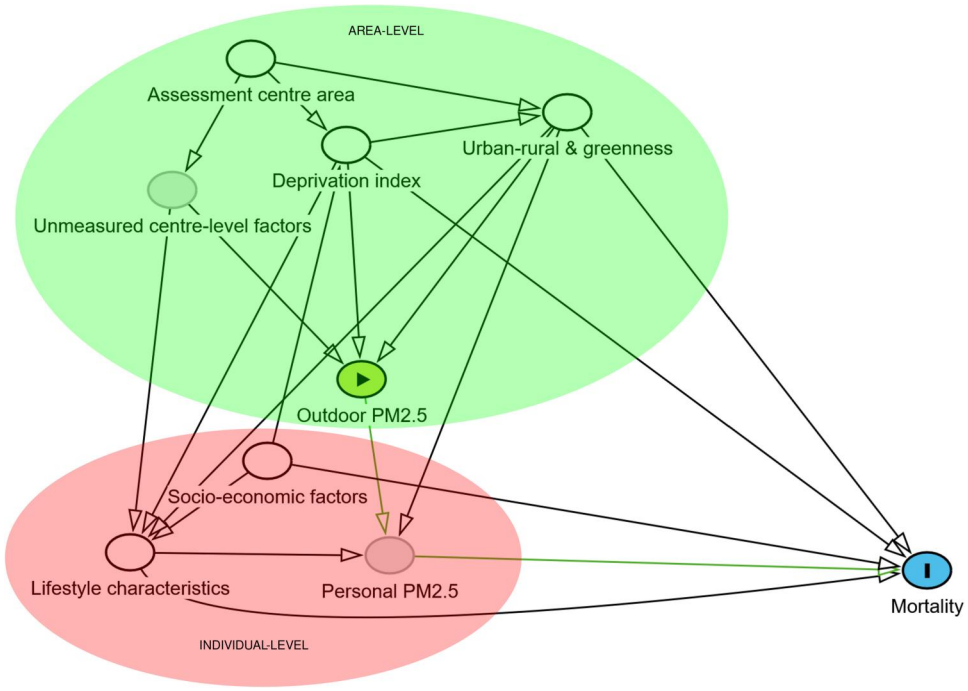

Figure 1. Directed acyclic graph (DAG) representing the assumed causal paths between exposure to fine particulate matter ($PM_{2.5}$) and mortality in the UK Biobank cohort.

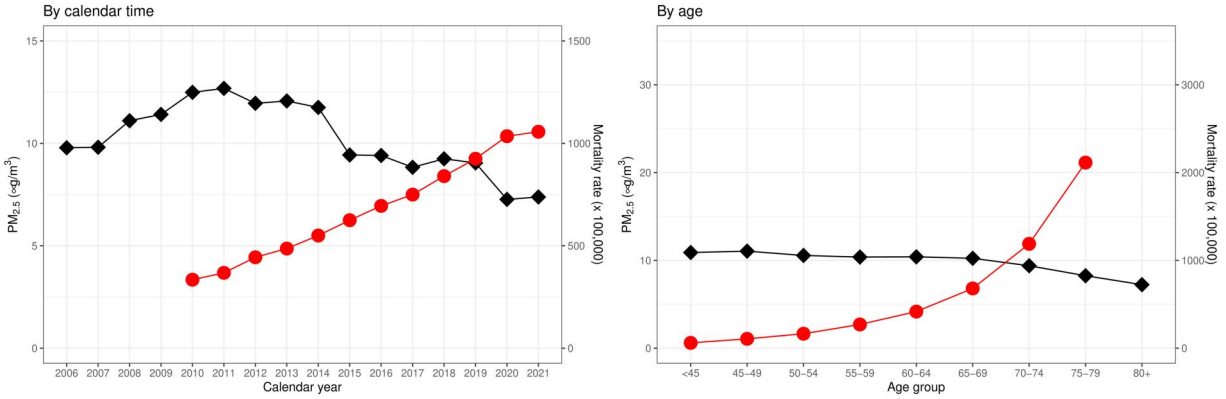

Figure 2. Trends of annual average exposure to fine particulate matter ($PM_{2.5}$, in μg/m^3, squared line) and mortality rates (per 100 000 person-years) by calendar time (left, dotted line) and age (right, dotted line) in the UK Biobank cohort.

Results

Descriptive analysis

The original dataset included 502 381 individuals. We excluded 4363 (0.87%) participants due to missing data in the exposure history, with a final cohort of 498 018 people. The participants were followed up for an average of 11.19 years, with a total of 5 575 253 person-years. During the follow-up, we observed 37 878 deaths for non-accidental causes.

The descriptive analysis of spatial and temporal patterns in $PM_{2.5}$ exposure and mortality rates can be useful to illustrate related confounding mechanisms and adjustment strategies. Figure 2 shows the time series of the distribution of annual $PM_{2.5}$ exposure and mortality rates over the timescales of calendar year and age. The contrasting trends in exposure and mortality risks indicate a threat of temporal confounding, and the need for an adequate control in the regression model. Figure 3 shows the average distribution of $PM_{2.5}$ against mortality rates calculated within assessment centre (see Supplementary Fig. S2 for their geographical locations). There was a south-to-north pattern, with higher $PM_{2.5}$ levels and lower mortality in centres belonging to the London area (Hounslow, Barts and Croydon) and partly in the South of England. The negative correlation makes the analysis prone to spatial confounding, which must be appropriately controlled for if not captured by area-level predictors.

Finally, Table 1 shows the distribution of average $PM_{2.5}$ exposure and mortality rates in categories of contextual and individual-level variables, indicating noticeable correlations. Specifically, higher area-level deprivation corresponded to higher mortality rates and strongly increasing exposure levels, while less urbanized areas were characterized by lower mortality rates and reduced air pollution. Similarly, residential greenness was associated with decreasing mortality and $PM_{2.5}$ concentrations. Individual-level variables show interesting patterns. For instance, average $PM_{2.5}$ exposure and mortality changed across categories of both socio-economic and lifestyle

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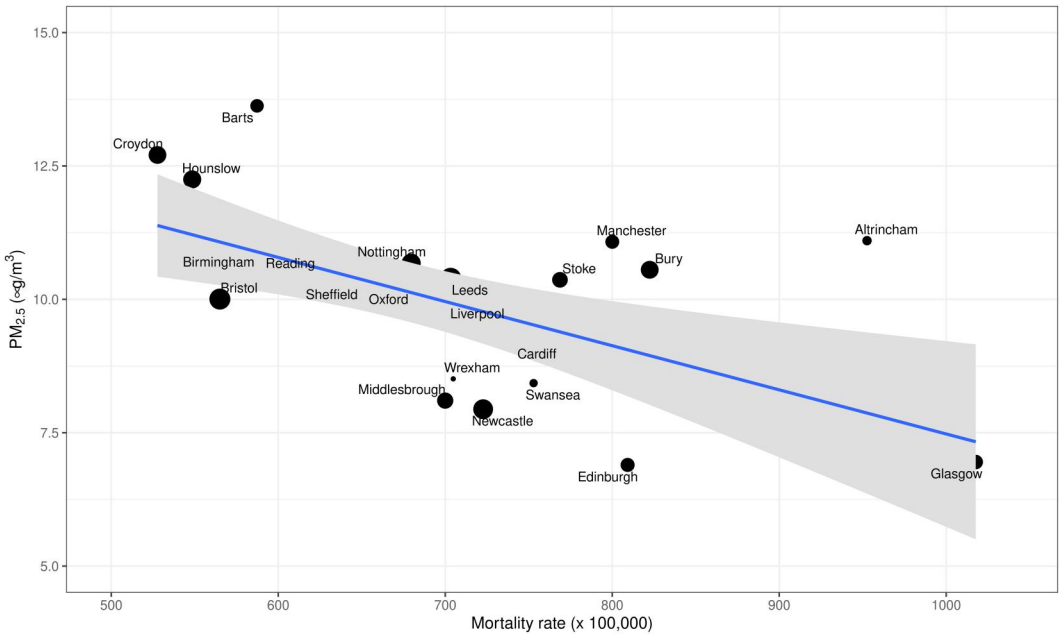

Figure 3. Scatterplot of average exposure to fine particulate matter ($PM_{2.5}$, in $\mu g/m^3$) and mortality rates (per 100 000 person-years) by assessment centre in the UK Biobank cohort.

factors, although part of these differences can be explained by age and location. While variations in exposure are minor, the striking differentials in mortality rates could still induce mild changes in the exposure-response associations.

Analysis of the directed acyclic graph

The assessment of the DAG in Fig. 1 indicates that all the measurable risk factors listed above must be included in the regression model to adjust for confounding. We highlight here some interesting aspects, however acknowledging that these considerations depend on the strong, untested, and (to some extent) subjective assumptions about the causal paths. First, control for assessment centre is important to limit spatial confounding, occurring primarily through the path involving unobserved area-level characteristics linked with differential outdoor $PM_{2.5}$ levels. Second, a lack of control for individual-level factors, represented by both socioeconomic conditions and lifestyle factors, can lead to confounding. Lifestyle characteristics can confound the association of outdoor $PM_{2.5}$ and mortality via a path involving unobserved area-level characteristics.

Regression analysis and control for confounding

The association between long-term exposure to $PM_{2.5}$ exposure and non-external mortality was first estimated with a fully adjusted model. The specification of this model provides control for the different types of confounding mechanisms mentioned above. First, the model directly adjusted for several personal characteristics and behaviours. Additionally, the inclusion assessment centre and year of birth as stratifying variables, together with sex, ensured a strong control for spatial and temporal patterns for $PM_{2.5}$ and death trends. Finally, additional control for contextual variables was provided by area-level deprivation, neighbour greenspace, and urban/rural classification. This main model (Model 1) reported an HR of 1.25 (95% CI: 1.06, 1.49) for a 10 $\mu g/m^3$ increase in the exposure, as shown in Table 2. The various confounding mechanisms were examined and quantified by fitting models with alternative specifications, with the corresponding estimates reported in the rest of the table.

The top part of Table 2 concerns temporal confounding, presenting models where calendar trends and age are adjusted in different ways. Specifically, age did not seem to act as a confounder, as the estimated HRs when controlling it directly through spline terms (Model 2) or not controlling for it at all (Model 3) were very close to the main model. The situation was different for calendar time: when using age as the time axis, calendar trends needed a strict adjustment through stratification by year (Model 4) or splines (Model 5). More importantly, the absence of control for calendar trends (Model 6) resulted in underestimation compared to the main model, with an HR of 1.18 (1.06–1.31).

The following models inform about different spatial confounding mechanisms, with more pronounced variations for different confounder adjustments. Specifically, the removal of control for assessment centre (Model 7), used in the main model as a stratifying variable, revealed a large confounding effect, with the risk reversing to an HR of 0.82 (0.76–0.87). This is consistent with the strong geographical correlation between baseline mortality and $PM_{2.5}$ exposure shown in Fig. 2. Also notable is the much narrower CIs compared to the main model, related to the wider exposure contrast obtained when removing assessment centre as a stratifying variable. The sensitivity analyses conducted for the inclusion of assessment centre (Supplementary Table S2) showed consistency among most methods (strata, indicator, and gamma random effects) except when normally distributed random effects were used.

Other spatial mechanisms can be related to variations in the distribution of measurable contextual risk factors, which can be assessed by removing each of them in turn from the model (Models 8–10). The comparison demonstrated a strong confounding effect of area-level deprivation, with the HR increasing to 1.51 (1.28–1.80) when excluding it from the model, while the control for greenspace and urban–rural produced minimal changes. Finally, the last two models examined the

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Table 1. Distributions of subjects, fine particulate matter ($PM_{2.5}$), and mortality across categories of contextual and individual-level variables in the UK Biobank cohort (see Supplementary Table S1 for further details)

Variable	Category	Count (%)	$PM_{2.5}$ average (SD)	Death rate (× 100 000)
Gender	Female	271 611 (54.5%)	10.79 (1.85)	518.13
	Male	226 407 (45.5%)	10.80 (1.83)	876.74
	Missing (%)	0 (0.0%)	NA	–
Townsend deprivation index (TDI)[a]	1st quintile	196 400 (39.4%)	10.40 (1.56)	594.31
	2nd quintile	180 916 (36.3%)	10.79 (1.75)	651.38
	3rd quintile	83 745 (16.8%)	11.31 (2.08)	792.83
	4th quintile	33 752 (6.8%)	11.84 (2.38)	1011.62
	5th quintile	3205 (0.6%)	11.82 (2.81)	1285.01
	Missing (%)	0 (0.0%)	–	–
Urban–rural classification	Urban	424 129 (85.2%)	10.98 (1.83)	689.37
	Town/fringe	37 611 (7.6%)	9.74 (1.53)	658.8
	Village/Rural	36 278 (7.3%)	9.70 (1.45)	584.34
	Missing (%)	0 (0.0%)	–	–
Greenspace[a]	1st quintile	82 036 (16.5%)	12.19 (2.07)	636.42
	2nd quintile	168 841 (33.9%)	11.01 (1.74)	713.31
	3rd quintile	127 046 (25.5%)	10.46 (1.52)	700.45
	4th quintile	78 132 (15.7%)	10.04 (1.47)	655.79
	5th quintile	41 963 (8.4%)	9.64 (1.44)	607.59
	Missing (%)	0 (0.0%)	–	–
Ethnic background	White	470 847 (94.5%)	10.71 (1.81)	692.56
	Other	27 171 (5.5%)	12.27 (1.81)	447.45
	Missing (%)	0 (0.0%)	–	–
Education	Low	85 753 (17.2%)	10.69 (1.76)	1245.11
	Professional	59 242 (11.9%)	10.66 (1.77)	789.52
	High school	190 183 (38.2%)	10.74 (1.75)	565.25
	College	162 840 (32.7%)	10.96 (2.00)	485.17
	Missing (%)	0 (0.0%)	–	–
Income	<18 000	117 126 (23.5%)	10.82 (1.81)	1156.19
	18 000–30 999	124 125 (24.9%)	10.72 (1.78)	739.34
	31 000–51 999	127 779 (25.7%)	10.74 (1.81)	494.24
	52 000–100 000	101 486 (20.4%)	10.82 (1.89)	390.28
	>100 000	27 502 (5.5%)	11.21 (2.13)	389.34
	Missing (%)	0 (0.0%)	–	–
Employment	Employed	288 733 (58.0%)	10.84 (1.86)	369.85
	Retired	166 525 (33.4%)	10.67 (1.78)	1176.45
	Other	42 760 (8.6%)	10.99 (1.94)	908.99
	Missing (%)	0 (0.0%)	–	–
Smoking status	Never	273 466 (54.9%)	10.75 (1.83)	480.1
	Previous	172 100 (34.6%)	10.82 (1.84)	831.45
	Current	52 452 (10.5%)	10.98 (1.91)	1253.93
	Missing (%)	0 (0.0%)	–	–
Smoking intensity[a]	0	275 782 (55.4%)	10.75 (1.83)	484.27
	≤10	60 933 (12.2%)	10.90 (1.86)	510.44
	10–29	104 544 (21.0%)	10.85 (1.85)	793.66
	30–60	48 488 (9.7%)	10.81 (1.85)	1518.47
	>60	8271 (1.7%)	10.85 (1.87)	2537.80
	Missing (%)	0 (0.0%)	–	–
Alcohol drinking status	Never	40 138 (8.1%)	11.05 (1.91)	986.13
	Occasionally	57 554 (11.6%)	10.93 (1.86)	805.66
	1–3 a month	55 588 (11.2%)	10.76 (1.81)	587.34
	1–2 a week	128 677 (25.8%)	10.67 (1.79)	604.3
	3–4 a week	114 975 (23.1%)	10.70 (1.82)	564.93
	Daily or almost	101 086 (20.3%)	10.91 (1.88)	768.01
	Missing (%)	0 (0.0%)	–	–
Waist-to-hip ratio[a]	Low	253 546 (50.9%)	10.77 (1.87)	528.81
	Medium	129 153 (25.9%)	10.78 (1.82)	749.01
	High	115 319 (23.2%)	10.87 (1.82)	937.97
	Missing (%)	0 (0.0%)	–	–
Physical activity (IPAQ[b] score)	Low	92 953 (18.7%)	10.78 (1.80)	793.6
	Moderate	193 796 (38.9%)	10.81 (1.88)	662.65
	High	211 269 (42.4%)	10.78 (1.83)	644.98
	Missing (%)	0 (0.0%)	–	–
Living alone	No	404 368 (81.2%)	10.74 (1.81)	607.5
	Yes	93 650 (18.8%)	11.02 (1.97)	998.36
	Missing (%)	0 (0.0%)	–	–

[a] Categorized for descriptive purposes in this table but used as continuous in the regression analysis.
[b] International Physical Activity Questionnaire.

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Table 2. Hazard ratio (HR) associated with an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ in the UK Biobank cohort, estimated from models with different adjustment strategies, with 95% confidence intervals (CI)

Main adjustment	Temporal adjustment		Model	HR (95% CI)
	Time axis	Additional term		
Fully-adjusted[a]	Calendar	Strata of age (year)	Model 1	1.25 (1.06–1.49)
	Calendar	Splines of age	Model 2	1.23 (1.04–1.47)
	Calendar	–	Model 3	1.25 (1.06–1.49)
	Age	Strata of calendar (months)	Model 4	1.24 (1.04–1.47)
	Age	Splines of calendar time	Model 5	1.27 (1.08–1.49)
	Age	–	Model 6	1.18 (1.06–1.31)
No assessment centre	Calendar	Strata of age (months)	Model 7	0.82 (0.76–0.87)
No deprivation index	Calendar	Strata of age (months)	Model 8	1.51 (1.28–1.80)
No urban–rural classification	Calendar	Strata of age (months)	Model 9	1.27 (1.07–1.51)
No greenspace	Calendar	Strata of age (months)	Model 10	1.24 (1.06–1.46)
No individual-level SES[b] factors	Calendar	Strata of age (months)	Model 11	1.25 (1.05–1.48)
No individual-level lifestyle factors	Calendar	Strata of age (months)	Model 12	1.34 (1.12–1.59)

[a] Cox model stratified by assessment centre, gender, and age (year of birth). Direct adjustment for: Townsend deprivation index (as continuous), urban–rural classification, greenspace (as continuous), ethnicity, education level, income level, employment status, smoking status, smoking intensity (packs-year, as continuous), alcohol consumption, waist-to-hip ratio (as continuous), IPAQ (International Physical Activity Questionnaire) score (physical activity proxy), living alone (marital status proxy).
[b] Socio-economic status factors: ethnicity, education level, income level, employment status.

role of individual-level risk factors, reporting estimates where socio-economic variables (Model 11) or other personal characteristics (Model 12) were removed, respectively. While the former did not seem to exert any confounding effect, the lack of control for physical and lifestyle factors seemed to lead to a noticeable overestimation, with an HR of 1.34 (1.12–1.59). An additional analysis where we evaluated the contribution from each of these factors separately indicated that lifestyle factors primarily operate collectively as a composite confounder, rather than in isolation (Supplementary Table S3).

Discussion

In this contribution, we illustrated and discussed confounding mechanisms in epidemiological studies on long-term risks associated with environmental factors, with a specific example on the association between $PM_{2.5}$ and mortality in the UKB. We performed a comprehensive assessment including descriptive analyses, theoretical considerations based on DAGs, and empirical results from regression models. The results are consistent and reveal various confounding patterns, offering insights as well as advice on specific adjustment strategies to be implemented in this context.

The most striking result is the strong spatial confounding linked with the lack of control for assessment centre, which represents a proxy for the residential area of the subject. Failing to adjust for it led to a strong confounding effect, with the HR reversing from 1.25 to 0.82, due to the strong correlation with both $PM_{2.5}$ concentrations and baseline mortality rates. It should be noted, however, that there is a trade-off between an aggressive spatial stratification and the reduction in exposure variation within risk sets that leads to reduced statistical power, as shown in the results. Some published analyses introduced spatial control, particularly through area-level random effects [15, 16], but others have not [17–21]. Our results, showing differential estimates depending on the distribution of random effects (Supplementary Table S2), are interesting and deserve further evaluation in future analyses. In any case, these results indicate that more attention needs to be devoted to controlling for spatial confounding in cohort studies on environmental risks. In our analysis, the negative direction of the association stemmed from the opposite geographical patterns of air pollution and death rates shown in Fig. 3, consistent with the 'Glasgow effect' previously reported in the literature, which represents an excess mortality in the Scottish population due to historical socio-economic circumstances [22].

Another interesting aspect is the issue of temporal confounding, requiring considerations of the choice of the time axis and the direct control for trends across other temporal dimensions. Our association estimates were invariant to the inclusion of age as a predictor, regardless of its specification, but highly sensitive to the exclusion of calendar year, leading to an overestimation of the health risks when the latter was excluded. These results can be explained by multiple aspects, including the use of time-varying exposure measures, the opposing trends in $PM_{2.5}$ and mortality over the study period, and the UKB being a closed (fixed) cohort, with the recruitment occurring in a short period and no replacement. These features motivated our choice regarding the selection of the time axis and the control of other temporal trends. While such a choice can change depending on the study setting and design, as well as on the temporal resolution of the exposure or other covariates, we emphasize the importance of appropriately accounting for temporal confounding in the analysis of long-term effects of environmental stressors.

One important topic addressed in this contribution is the confounding mechanisms related to individual-level factors on health risks associated with air pollution. The question is motivated by the lack of individual information in administrative health databases often used to perform large population-based cohort analyses [23, 24], other than basic socio-economic indices (e.g. education and income) and ethnicity. In particular, the role of lifestyle characteristics is currently debated, with a line of thought asserting that these factors should not be controlled for, as they are not correlated with area-level pollution levels [25]. Both theoretical arguments and empirical results presented here put such an argument into question. First, the DAG in Fig. 1 demonstrated that lifestyle factors can confound through spatial correlation with pollution levels, induced by the presence of unobserved area-level characteristics. Second, the regression analysis indicated a noticeable increase in HR when removing lifestyle variables, leading to an overestimation of the risk.

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This finding aligns with previous studies that found strong air pollution effects when accounting for individual-level covariates [26–28]. This result is also consistent with the descriptive analysis.

Some limitations must be acknowledged. First, the results presented here are specific to the UKB. Nonetheless, while different patterns can be found in other cohorts, general considerations about confounding mechanisms would still be relevant. Second, the UKB database presents some limitations, in particular the fact that most of the variables were collected only at recruitment and that the residential locations of the subjects are not made available to the users, requiring the use of assessment centre as a proxy for geographical areas. Both issues surely introduce errors and imprecision, although again, this fact does not affect the general considerations made here about confounding. Third, while we did not investigate the impact of potential interactions between covariates in this analysis, exploring such effects would be a valuable direction for future research. Moreover, it must be stressed that this contribution aimed to identify and discuss various confounding patterns in cohort studies on the health risks of environmental stressors, albeit without making use of and discussing complex causal inference methodologies to address them.

In conclusion, this case-study assessment presents and discusses various confounding effects in cohort studies on long-term risks of environmental exposures. The results showed consistent patterns between descriptive analyses, theoretical arguments from DAGs, and regression models. These findings offer insights into approaches to control for spatial differences and temporal trends in exposure and risks, as well as the need to adjust for a set of potential confounders, including lifestyle variables.

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Author contributions

J.V.: researched literature, conception and design of the study, analysis and interpretation of data, writing of first manuscript, approval of the version to be published. L.M: interpretation of data, critical revision of manuscript for intellectual content, approval of the version to be published. M. S.: interpretation of data, approval of the version to be published. C.F.S.N.: design of the study, critical revision of manuscript for intellectual content, approval of the version to be published. A.G.: acquisition and analysis of data, interpretation of the data, study supervision, critical revision of manuscript for intellectual content, approval of the version to be published.

Supplementary data

Supplementary data is available at *IJE* online.

Conflict of interest

None declared.

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Data availability

The original full R code used to perform the analysis is available in a GitHub repo (https://github.com/gasparrini/UKB-confounding), and it can be used alongside the synthetic datasets that resemble the original UK Biobank data. The actual database of the UK Biobank can be accessed via an application through the UK Biobank online Access Management System (AMS) (https://www.ukbiobank.ac.uk/). The $PM_{2.5}$ exposure dataset was expressly linked in this analysis and will be fully attached to the main database and released in the UK Biobank repository.

Use of Artificial Intelligence (AI) Tools

During the preparation of this work, the authors used ChatGPT3.5/4 to improve the clarity and flow of the writing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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