

Impact of social determinants, lifestyle and air pollution on the allergic diseases and comorbidities: A multi-state analysis of a prospective cohort

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ABSTRACT

Background: The longitudinal progression from health to single allergic diseases and subsequently to comorbidities and mortality remains understudied in adults. This study aimed to investigate the impact of social determinants, lifestyle factors, and air pollution on multi-state allergic disease progression.

Method: A total of 109,018 adults without allergic diseases at recruitment were extracted from the UK Biobank database. A multi-state Markov proportional hazards model was used to assess the association between multi-dimensional factors and allergic disease progression. The model specifically analyzed transitions from baseline health to single allergic disease onset, subsequent comorbidities, and mortality.

Results: Over a median follow-up of 11.2 years, 13,815 participants developed at least one allergic disease, 428 progressed to allergic comorbidities, and 18,607 died. Multi-state modeling revealed risk patterns across different disease stages within adult allergic disease trajectories. Specifically, transitions from health to single allergic disease onset and from single allergic disease to mortality were significantly associated with lower socioeconomic status (SES), higher Townsend Deprivation Index (TDI), history of violence victimization, smoking, and NO₂ exposure. Regarding progression to allergic comorbidities and mortality among comorbid patients, healthier dietary patterns exhibited significant protective effects. PM₁₀ exposure and lower SES were identified as significant risk factors for development of comorbidities.

Conclusion: The onset, progression, and mortality of adult allergic diseases are influenced by multidimensional factors, including social determinants, lifestyle, and air pollution. These findings highlight the critical role of enhancing socioeconomic equity, promoting healthy lifestyles, and controlling air pollution in preventing allergic diseases and mitigating subsequent adverse outcomes.

Impact Statement

This study demonstrates that the onset, comorbidity progression, and mortality of adult allergic diseases are driven by social determinants, lifestyle behaviors, and air pollution. These findings underscore the urgent need for multi-level prevention framework, encompassing population-level health equity, individual behavioral interventions, and environmental governance, to disrupt the disease progression chain and

reduce the burden of adult allergic diseases.

1. Introduction

Allergic diseases, including atopic dermatitis (AD), food allergy, allergic rhinitis (AR), and asthma, are immune-mediated disorders affecting approximately 20 % of the global population and posing a

Abbreviations: AD, Atopic dermatitis; AR, allergic rhinitis; UKB, UK Biobank; IgE, Immunoglobulin E; HR, Hazard Ratio; CI, Confidence Interval; BMI, Body Mass Index; ESCAPE, The European Study of Cohorts for Air Pollution Effects; TDI, Townsend Deprivation Index; PM, Particulate Matter; NO₂, Nitrogen Dioxide; NO_x, Nitrogen Oxide; ICD, International Classification of Diseases; LUR, Land Use Regression; MICE, multiple imputation by chained equations; AIC, Akaike information criterion; BIC, Bayesian Information Criterion; SD, Standard Deviation; LASSO, Least Absolute Shrinkage and Selection Operator; AUC, Areas Under the Receiver Operating Characteristic Curve; OR, Odds Ratio; SES, Socioeconomic status; LCA, latent class analysis; HPA, hypothalamic-pituitary-adrenal.

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significant public health challenge (Pedersen et al., 2020). Among these, AD is the most prevalent chronic inflammatory skin disease, impacting 1–10 % of adults worldwide (Hay et al., 2014). Concurrently, AR exhibits a prevalence of 1–40 %, while asthma affects approximately 4 % of the global population (Brożek et al., 2017; Khan et al., 2023; Singh et al., 2019). Characterized by immune dysregulation and barrier dysfunction, these conditions often manifest as comorbidities (e.g., AD patients frequently develop concomitant AR or asthma) (Bousquet et al., 2023; Brożek et al., 2017; Yaneva and Darlenski, 2021). Given their high prevalence and frequent comorbidities, systematically identifying key risk factors for allergic disease onset and progression is critical to developing targeted prevention strategies and reducing the global disease burden.

Existing evidence indicates that allergic disease onset arises from multidimensional determinants. Social determinants, such as socioeconomic status (SES), residential duration, and violent victimization, drive allergic disease onset through disparities in healthcare resources and health-promoting behaviors, long-term environmental exposure, and stress-induced immune dysregulation (He et al., 2024; Nash et al., 2023; Uphoff et al., 2015; Wang, 2023; Wong and Chew, 2024). Lifestyle factors (BMI, smoking status, physical inactivity, and unhealthy dietary patterns) exacerbate allergic diseases risk through oxidative stress, systemic inflammation, and gut microbiota-immune axis dysregulation (Fan et al., 2024; Testa et al., 2020; Ziyab, 2017). Additionally, air pollutants contribute to disease onset by inducing epithelial barrier damage, IgE-mediated sensitization, and aberrant immune cell differentiation (Burte et al., 2018; Eguiluz-Gracia et al., 2020; Pan et al., 2023). Notably, these factors interact multidimensionally to modulate individual susceptibility to environmental pollutants: high-SES individuals may mitigate pollution-related risks through socioeconomic-behavioral pathways, including residential air purification and low-exposure commuting practices; healthy lifestyles (e.g., Mediterranean-style diets and regular exercise) attenuate pollutant toxicity by enhancing antioxidant capacity and facilitating inflammatory resolution (Hajat et al., 2021; Li et al., 2023; Wang et al., 2022; Zhu et al., 2024). Thus, integrating analysis of these factors enables systematic assessment of the socio-behavioral-environmental interactions in allergic disease pathogenesis, providing translational evidence for implementable prevention strategies.

However, while epidemiological studies have established associations linking various risk factors to the incidence of specific allergic diseases, their roles in shaping longitudinal disease trajectories and distinct progression stages in adults remain poorly characterized. This knowledge gap partly reflects methodological constraints of conventional statistical approaches. Specifically, Cox proportional hazards models that are predominantly used in cohort studies fail to adequately characterize time-dependent transition dynamics throughout disease progression. In contrast, multi-state models can differentially quantify factor effects at each transitional stage along the disease trajectory, explicitly capturing pathways from baseline health to initial onset, subsequent comorbidity development, and ultimately mortality. Based on established epidemiological evidence, we hypothesize that multidimensional factors exert stage-specific effects on the dynamic progression of adult allergic diseases. Exploring these differential effects is critical for developing stage-targeted interventions across the disease continuum.

Accordingly, this study employed a multi-state model to investigate transitions from health to incident allergy, progression to comorbidities, and subsequent mortality, as well as to assess associations between multidimensional factors and distinct transitional phases. The findings will elucidate adult allergic disease trajectories and inform the formulation of scientific hypotheses and prevention strategies for allergic disorders.

2. Methods

2.1. Study population

The data used in this study were extracted from the UKB, a prospective cohort study comprising 502,366 adults aged 37–73 years recruited from the general UK population at baseline (March 2006–October 2010). Participants attended one of 22 assessment centers in England, Scotland, and Wales, completing nurse-administered electronic questionnaires, undergoing physical examinations, and providing biospecimens (Sudlow et al., 2015). Follow-up commenced at baseline and continued until death, loss to follow-up, or the end of the follow-up period (1 February 2020). Participants lost to follow-up were classified as left-censored controls.

To control for potential confounders and ensure data quality, we applied strict exclusion criteria. From the initial cohort ($n = 502,366$), we excluded individuals who: (1) had baseline diagnoses of AD, AR or asthma ($n = 98,807$); (2) developed multiple allergic conditions concurrently (i.e., diagnosed on the same day; $n = 421$), as determining the temporal sequence of onset was infeasible; (3) had missing data for air pollution exposure or key variables ($n = 59,038$); (4) had pre-existing severe chronic diseases or conditions (detailed in Table A.1) at baseline ($n = 222,385$), aligning with exclusion criteria from prior epidemiological studies to establish a relatively healthy cohort (Cheng et al., 2022; He et al., 2024); (5) experienced outcome events (incident allergic diseases, comorbidities or mortality) after the follow-up period ($n = 12,697$). Consequently, a total of 109,018 participants were included in the final study population (Fig. 1).

2.2. Assessment of outcomes

The primary outcomes included incident allergic diseases (AD, AR, and asthma), development of allergic comorbidities (defined as concurrent diagnosis of ≥ 2 allergic diseases), and all-cause mortality during follow-up. Corresponding ICD-10 codes and UKB data fields are detailed in Table A.1. Incident cases of allergic diseases were identified using UKB's first occurrence data, whereas all-cause deaths were confirmed via linkage to National Death Registries. To mitigate potential confounding from the COVID-19 pandemic, the follow-up period ended on 1 February 2020. Notably, food allergies were excluded as an outcome owing to limited data availability (UKB's first occurrence data lacks specific ICD-10 codes for food allergies and relevant questionnaire items are absent).

2.3. Assessment of variables

Variables were selected based on established associations with allergic disease onset and progression in prior literature (Chong and Chew, 2018; Fan et al., 2024; Nash et al., 2023; Testa et al., 2020; Wang, 2023), categorized into 3 dimensions: 1) demographic characteristics comprising age and sex; 2) social determinants incorporating violent victimization, residential duration, area-level Townsend Deprivation Index (TDI), and individual SES derived through latent class analysis (LCA) using household income, educational attainment, and occupational status; and 3) modifiable lifestyle factors including body mass index (BMI) category, smoking status, secondhand tobacco exposure, alcohol consumption, dietary quality score, and physical activity level (detailed in Table A.2). Most variables were assessed via self-reported baseline questionnaires. The dietary score was computed based on the consumption frequency of the top 5 most commonly consumed food categories (Bradbury et al., 2020; Wang et al., 2021). Other potential variables (e.g., genetic factors, pet exposure) were excluded due to limited relevance to the socio-behavioral-environmental focus or inadequate data availability within the UKB (Chong and Chew, 2018; Zhu et al., 2024).

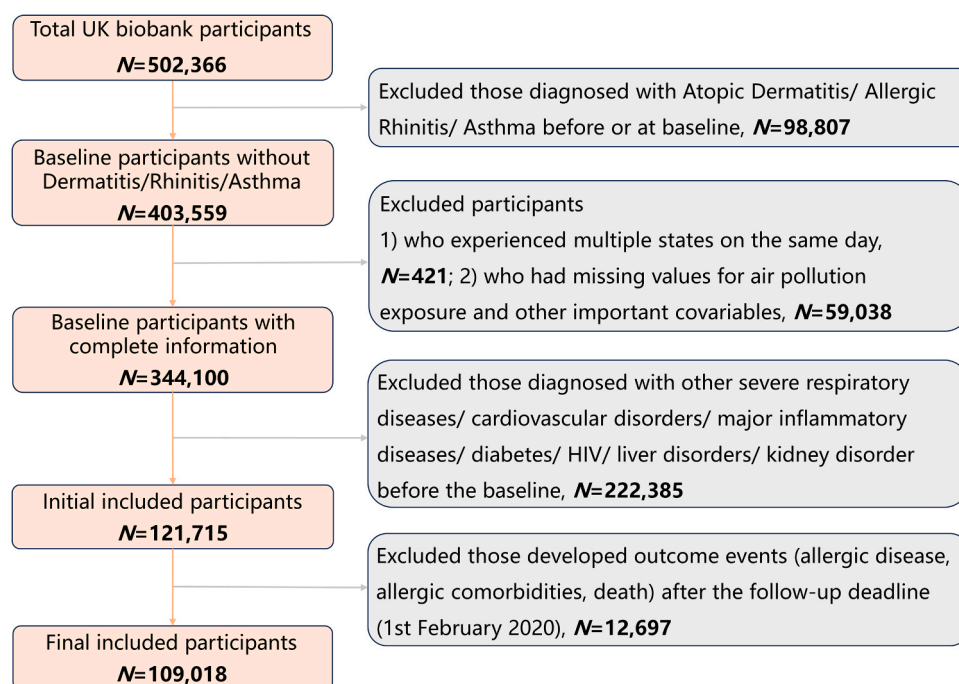


Fig. 1. The flow chart of the UK Biobank participants included and excluded in the study.

2.4. Assessment of air pollution

Annual air pollutant concentrations ($PM_{2.5}$, PM_{10} , NO_2 and NO_x) were estimated using land use regression (LUR) models from the ESCAPE project (Weng et al., 2022), which integrate traffic, land use, and topography data via geographic information systems (Doiron et al., 2019). Model performance was validated through leave-one-out cross-validation, yielding R^2 values of 68–82 % (Eeftens et al., 2012). The UKB utilized residential addresses to assign exposure values to each participant. Some pollutants had single-year data (2010), while others spanned multiple years (2005–2010). The 2010 concentrations were derived from a robust ESCAPE model linked to baseline addresses. Conversely, estimates for 2005–2007 were obtained from EU-wide maps at 100×100 m resolution (Beelen et al., 2013). To ensure methodological consistency and prevent bias from integrating estimates generated by different models across temporal periods, we employed the 2010 exposure estimates for the four pollutants, adhering to UKB methodological guidelines. All concentrations are reported in $\mu g/m^3$.

2.5. Statistical analysis

LCA, a probabilistic parametric mixture modeling approach, explicitly estimates latent class prevalence and item-response probabilities under distributional assumptions while accounting for measurement error (Collins and Lanza, 2010). In this study, LCA was employed to identify distinct SES latent classes based on response patterns across 3 variables: total household income, highest educational attainment, and employment status, which have been validated as robust proxies for individual-level socioeconomic stratification (Li et al., 2023). Variable definitions and UKB data sources are detailed in Table A.2. The optimal model was selected based on the BIC (lower values indicating better parsimony), class interpretability (clinical relevance of additional classes), and class prevalence ($\geq 5\%$ of the sample to ensure replicability) (Soussi et al., 2022).

Baseline characteristics were summarized using means (SDs) for continuous variables and proportions for categorical variables. We employed multi-state Markov models to investigate associations between multidimensional factors and disease transitions. Two model

structures were implemented: a 4-state model including 5 different transitions, encompassing progression from a healthy state to the onset of specific allergic diseases, development of allergic comorbidities, and mortality (Fig. 2a); and a 6-state model stratifying single allergic diseases into AD, AR, and asthma, with 11 possible transitions (Fig. 2b). These models, extending competing risk survival analysis, simultaneously estimate transition hazards from an initial state to intermediate events and subsequent final states, explicitly delineating temporal sequences while addressing competing risks (Wang et al., 2023). This type of analysis enables clear delineation of the time series and addresses competing risks during disease progression. The estimated probability of entering a future state depends solely on the current state. Each transition was modeled using Cox proportional hazards models.

First, multi-state Markov models assessed the effects of demographic characteristics, social determinants and lifestyle factors on both 4-state and 6-state transition structures. Subsequently, to investigate air pollution impacts, 3 distinct analytical models were developed for each pollutant: Model 1 included individual pollutants without adjustment; Model 2 adjusted for baseline demographics; and Model 3 further adjusted for all variables, including demographic characteristics, social determinants and lifestyle factors, but excluded TDI. Models estimated transition-specific HRs and 95 % CIs for all variables (De Wreede et al., 2010), with pollutant HRs representing the relative risk per $1 \mu g/m^3$ increase in pollutant concentration.

LASSO regression with 10-fold cross-validation was used to develop predictive models for allergic disease incidence and mortality. The cohort was randomly split into training ($n = 87,293$) and validation ($n = 21,725$) sets (4:1 ratio). Discriminative ability was evaluated using AUCs for fitted and predicted values. Additionally, we conducted a series of subgroup and sensitivity analyses: First, we examined population heterogeneity by stratifying analyses by sex and age subgroups, and further employed independent two-sample Z-tests for between-group effect size (HRs) comparisons and multivariable interaction models with pollutant $\times$ subgroup terms to quantify effect modification. Second, multiplicative interaction terms (pollutants [$PM_{2.5}/NO_2$] $\times$ [social determinants/lifestyle factors]) were incorporated into Model 3 to assess potential effect modification between air pollution and social determinants/ lifestyle factors. Third, to validate result stability and to

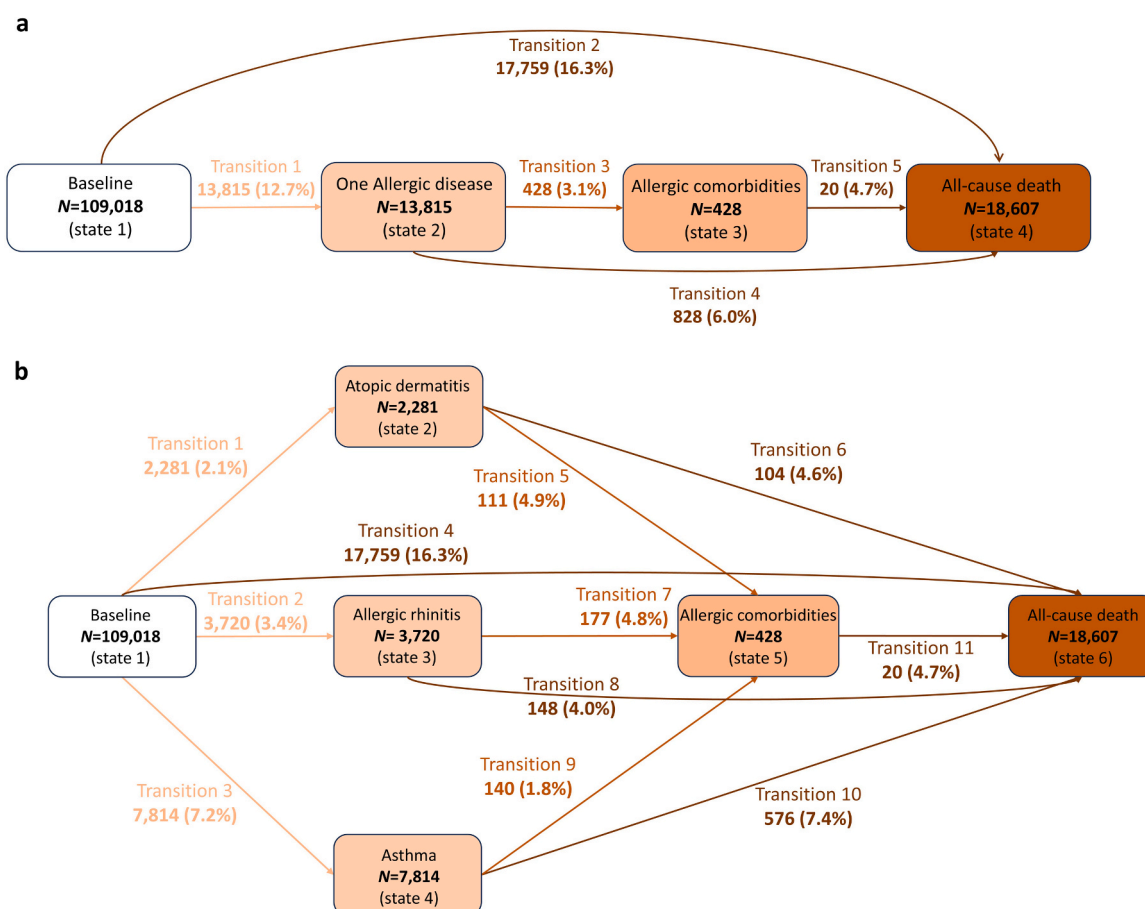


Fig. 2. Numbers (percentages) of participants in 4-state transitions (a) and 6-state transitions (b) from healthy baseline to onset of one allergic disease, allergic comorbidities and all-cause death.

evaluate the impact of missing data handling, we performed multiple imputation (MI) for 4 pollutants ($PM_{2.5}$, PM_{10} , NO_2 , NO_x) and 6 variables (TDI, residential duration, smoking status, alcohol drinking status, diet scores, and BMI, see details in the [Supplementary Methods](#)). Using this imputed dataset ($n = 165,291$), we repeatedly performed the analytical models, including both models with all variables except pollutants and the Model 3. Fourth, to investigate the influence of TDI on pollutant effects, we conducted Pearson correlation analyses between all variables (including TDI) and pollutants, and performed sensitivity analyses incorporating TDI as a variable in Model 3. Finally, to assess potential temporal bias or deviation from single-year exposure assessment, we conducted two time-dependent sensitivity analyses: restricting follow-up duration to the first 5 years and excluding cases onset within the first 5 years of follow-up. Analyses were performed in R (v4.3.2), with the LCA constructed via the “depmixS4” package, the MICE performed by the “mice” package and multi-state models executed using the “msm” package.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 109,018 participants (57.00 % female) are summarized in [Table 1](#), including demographics, social determinants, lifestyle factors, and air pollutant exposures. During follow-up, 13,815 individuals (12.7 %) developed at least one allergic disease (state 2) from the baseline healthy state (state 1), 428 (3.1 %) progressed to allergic comorbidities (state 3), and 18,607 (17.1 %) died (state 4), as presented in the 4-state transitions ([Fig. 2a](#)). Among those

who died, 17,759 (95.4 %) had no allergic disease diagnosis, 828 (4.5 %) had one allergic disease, and 20 (0.1 %) had allergic comorbidities. Baseline characteristics stratified by disease state are also provided in [Table 1](#).

In the 6-state transition model ([Figs. 2b](#)), 2,281 (2.1 %) healthy participants developed AD (state 2), 3720 (3.4 %) developed AR (state 3), and 7814 (7.2 %) developed asthma (state 4). Participants with initial AD or AR had higher rates of progression to comorbidities (state 5, $n = 111$, 4.9 % and $n = 177$, 4.8 %, respectively) compared to those with initial asthma ($n = 140$, 1.8 %). However, participants who first developed asthma had a higher likelihood of mortality ($n = 576$, 7.4 %) compared to those who first developed AD ($n = 104$, 4.6 %) or AR ($n = 148$, 4.0 %).

3.2. Social determinants, lifestyle factors and progression of allergic diseases

LCA was performed using 3 validated individual-level SES indicators: household income, educational attainment, and employment status. Model selection evaluated BIC statistics for 2–7 latent classes ([Figure A.1](#)), prioritizing the lowest BIC while ensuring relative parsimony, class-specific item-response probabilities and socioeconomically meaningful stratification patterns. This process derived 4 SES categories: high (5.08 %, $n = 5538$), medium-high (59.75 %, $n = 65,138$), medium-low (14.95 %, $n = 16,298$), and low (20.23 %, $n = 22,054$), as visualized in [Fig. 3](#).

In the 4-state transition model excluding air pollutants ([Fig. 4](#)), several variables showed significant associations with disease transitions. From health to single allergic disease, risk factors included male

Table 1

The characteristics of the study population with different final states during follow-up.

	Overall (N = 109,018)	Free of any allergic diseases, alive (N = 77,444)	Free of any allergic diseases, dead (N = 17,759)	Diagnosed with one allergic disease, alive (N = 12,559)	Diagnosed with one allergic disease, dead (N = 828)	Have allergic comorbidity, alive (N = 408)	Have allergic comorbidity, dead (N = 20)
Pollutants ($\mu\text{g}/\text{m}^3$), mean (SD)							
PM _{2.5}	9.99 (1.06)	9.96 (1.05)	10.05 (1.08)	10.04 (1.05)	10.15 (1.06)	10.09 (1.05)	10.12 (0.51)
PM ₁₀	16.24 (1.90)	16.23 (1.91)	16.25 (1.88)	16.29 (1.89)	16.37 (1.90)	16.43 (2.00)	17.08 (1.98)
NO ₂	26.74 (7.72)	26.67 (7.77)	26.83 (7.67)	26.96 (7.50)	27.48 (7.39)	26.98 (7.20)	25.86 (3.01)
NO _x	44.04 (15.63)	43.75 (15.50)	44.67 (16.16)	44.77 (15.74)	45.68 (14.49)	44.97 (15.35)	42.79 (6.84)
Age (year), mean (SD)	55.26 (8.28)	53.22 (7.76)	62.08 (6.38)	57.62 (7.88)	62 (6.39)	57.32 (7.82)	60.76 (7.70)
Sex, n (%)							
Female	62,143 (57.00)	46,973 (60.65)	7030 (39.59)	7544 (60.07)	335 (40.46)	255 (62.50)	6 (30.00)
Male	46,875 (43.00)	30,471 (39.35)	10,729 (60.41)	5015 (39.93)	493 (59.54)	153 (37.50)	14 (70.00)
TDI, mean (SD)	-1.40 (3.00)	-1.52 (2.93)	-1.04 (3.20)	-1.24 (3.06)	-0.46 (3.33)	-1.18 (3.07)	-0.56 (3.13)
SES level, n (%)							
Low	22,052 (20.23)	10,173 (13.14)	7604 (42.82)	3721 (29.63)	434 (52.42)	111 (27.21)	9 (45.00)
Lower-middle	16,297 (14.95)	12,295 (15.88)	1964 (11.06)	1897 (15.10)	83 (10.02)	56 (13.73)	2 (10.00)
Upper-middle	65,134 (59.75)	50,135 (64.74)	7875 (44.34)	6598 (52.54)	297 (35.87)	220 (53.92)	9 (45.00)
High	5535 (5.07)	4841 (6.24)	316 (1.78)	343 (2.73)	14 (1.69)	21 (5.14)	0 (0)
Violence victim, n (%)							
Never	27,807 (25.51)	23,316 (30.11)	1264 (7.12)	3042 (24.22)	74 (8.94)	110 (26.96)	1 (5.00)
Do not know	74,509 (68.35)	48,532 (62.67)	16,252 (91.51)	8696 (69.24)	739 (89.25)	272 (66.67)	18 (90.00)
Prefer not to answer	46 (0.04)	35 (0.05)	3 (0.02)	7 (0.06)	0 (0)	1 (0.25)	0 (0)
Yes	6656 (6.11)	5561 (7.17)	240 (1.35)	814 (6.48)	15 (1.81)	25 (6.12)	1 (5.00)
Residence duration, n (%)							
Short (<10 years)	37,635 (34.52)	28,509 (36.81)	4724 (26.60)	4007 (31.91)	255 (30.80)	135 (33.09)	5 (25.00)
Long ($\geq$ 10 years)	71,383 (65.48)	48,935 (63.19)	13,035 (73.40)	8552 (68.09)	573 (69.20)	273 (66.91)	15 (75.00)
Education level, n (%)							
Low (None of the above)	15,010 (13.77)	7217 (9.32)	4938 (27.81)	2483 (19.77)	289 (34.90)	77 (18.87)	6 (30.00)
Middle (National exams)	25,878 (23.74)	18,993 (24.52)	3749 (21.11)	2869 (22.84)	168 (20.29)	92 (22.55)	7 (35.00)
High (College/ University/ Vocational)	68,130 (62.49)	51,234 (66.16)	9072 (50.08)	7207 (57.39)	371 (44.81)	239 (58.58)	7 (35.00)
Annual household income, n (%)							
Do not know/Low (<£18,000)	32,185 (29.52)	18,354 (23.70)	8422 (47.42)	4793 (38.16)	461 (55.68)	144 (35.29)	11 (55.00)
Middle (£18,000, £100,000)	70,477 (64.65)	53,548 (69.14)	8958 (50.44)	7369 (58.68)	351 (42.39)	242 (59.31)	9 (45.00)
High ($\geq$ £100,000)	6356 (5.83)	5542 (7.16)	379 (2.14)	397 (3.16)	16 (1.93)	22 (5.40)	0 (0)
Employment status, n (%)							
None of the above/ Unemployed	9739 (8.93)	62,16 (8.03)	1955 (11.01)	1400 (11.15)	113 (13.65)	54 (13.24)	1 (5.00)
Retired	29,297 (26.87)	14,502 (18.73)	9747 (54.88)	4438 (35.34)	468 (56.52)	134 (32.84)	8 (40.00)
Paid or self-employed	69,982 (64.20)	56,726 (73.24)	6057 (34.11)	6721 (53.51)	247 (29.83)	220 (53.92)	11 (55.00)
BMI level, n (%)							
Normal (<25 kg/m ²)	42,999 (39.44)	33,983 (43.88)	50,51 (28.44)	3626 (28.87)	222 (26.81)	112 (27.45)	5 (25.00)
Overweight (25,30 kg/m ²)	45,257 (41.51)	32,037 (41.37)	7485 (42.15)	5220 (41.56)	324 (39.13)	183 (44.85)	8 (40.00)
Obese ($\geq$ 30 kg/m ²)	20,762 (19.05)	11,424 (14.75)	5223 (29.41)	3713 (29.57)	282 (34.06)	113 (27.70)	7 (35.00)
Smoking status, n (%)							
Never or previous	97,503 (89.44)	70,770 (91.38)	14,498 (81.64)	11,218 (89.32)	640 (77.29)	363 (88.97)	14 (70.00)
Current	11,515 (10.56)	6674 (8.62)	3261 (18.36)	1341 (10.68)	188 (22.71)	45 (11.03)	6 (30.00)
Tobacco exposure, n (%)							
Prefer not to answer	6873 (6.30)	4402 (5.68)	1321 (7.44)	1052 (8.38)	69 (8.33)	27 (6.62)	2 (10.00)
Do not know	8345 (7.65)	4369 (5.64)	2755 (15.51)	1019 (8.11)	162 (19.57)	34 (8.33)	6 (30.00)
No	73,840 (67.73)	54,929 (70.93)	10,307 (58.04)	7917 (63.04)	425 (51.33)	254 (62.25)	8 (40.00)
Yes ($\geq$ 1 h/w)	19,960 (18.32)	13,744 (17.75)	3376 (19.01)	2571 (20.47)	172 (20.77)	93 (22.80)	4 (20.00)

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Table 1 (continued)

	Overall (N = 109,018)	Free of any allergic diseases, alive (N = 77,444)	Free of any allergic diseases, dead (N = 17,759)	Diagnosed with one allergic disease, alive (N = 12,559)	Diagnosed with one allergic disease, dead (N = 828)	Have allergic comorbidity, alive (N = 408)	Have allergic comorbidity, dead (N = 20)
Alcohol drinking status, n (%)							
Unhealthy (≥ 16 g/d)	34,845 (31.96)	23,977 (30.96)	6524 (36.74)	3879 (30.89)	322 (38.89)	137 (33.58)	6 (30.00)
Healthy (< 16 g/d)	74,173 (68.04)	53,467 (69.04)	11,235 (63.26)	8680 (69.11)	506 (61.11)	271 (66.42)	14 (70.00)
†Diet score, n (%)							
0	3542 (3.25)	2392 (3.09)	689 (3.88)	405 (3.22)	40 (4.83)	14 (3.43)	2 (10.00)
1	13,344 (12.24)	9322 (12.04)	2432 (13.69)	1420 (11.31)	109 (13.16)	57 (13.97)	4 (20.00)
2	25,079 (23.00)	17,596 (22.72)	4381 (24.67)	2794 (22.25)	214 (25.85)	89 (21.81)	5 (25.00)
3	29,948 (27.47)	21,152 (27.31)	4882 (27.49)	3590 (28.59)	205 (24.76)	113 (27.70)	6 (30.00)
4	25,543 (23.43)	18,550 (23.95)	3729 (21.00)	2975 (23.69)	188 (22.71)	98 (24.02)	3 (15.00)
5	11,562 (10.61)	8432 (10.89)	1646 (9.27)	1375 (10.94)	72 (8.69)	37 (9.07)	0 (0)
Physical activity status, n (%)							
Do not know	18,104 (16.60)	11,884 (15.35)	3477 (19.58)	2495 (19.87)	171 (20.65)	73 (17.89)	4 (20.00)
Unhealthy	17,005 (15.60)	11,277 (14.56)	3452 (19.44)	2027 (16.14)	174 (21.01)	72 (17.65)	3 (15.00)
Healthy	73,909 (67.80)	54,283 (70.09)	10,830 (60.98)	8037 (63.99)	483 (58.34)	263 (64.46)	13 (65.00)

†The healthy dietary score was computed, according to the consumption frequency of five commonly eaten food groups and the corresponding diet factors were vegetable intake ≥ 4 tablespoons/day; fruit intake ≥ 3 pieces/day; fish intake ≥ 2 /week; unprocessed red meat intake < 2 /week; and processed meat intake < 2 /week. Each one point was given for each favorable diet factor, and the healthy diet score ranged from 0 to 5.

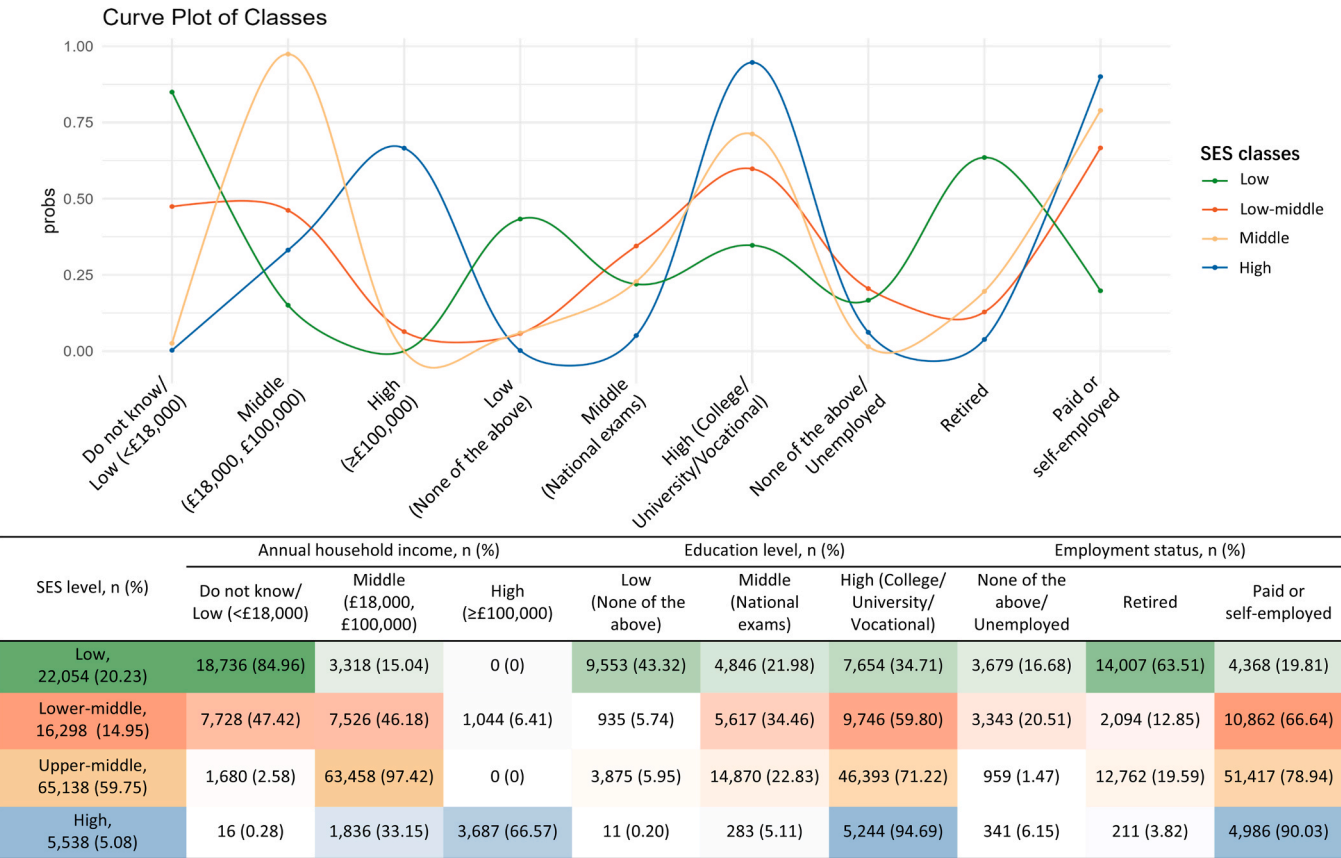


Fig. 3. High, upper-middle, lower-middle, low socioeconomic status (SES) latent class trajectories and their practical definitions.

sex, older age, lower SES, violent victimization, shorter residential duration, higher BMI, smoking, and insufficient physical activity. Meanwhile, healthy dietary patterns (HR: 0.911 [0.842, 0.986]) reduced the risk of allergic comorbidity progression. For mortality, lower SES, violent victimization, higher BMI, physical inactivity, and unhealthy dietary patterns increased risk in healthy individuals. In allergic patients, male sex (HR: 1.077 [1.064, 1.090]), older age (HR: 1.868 [1.602, 2.178]), lower SES (HR: 0.756 [0.699, 0.817]), smoking (HR:

2.596 [2.186, 3.084]), and violent victimization (HR: 1.091 [1.001, 1.190]) elevated mortality risk. Additionally, female sex (HR: 5.004 [1.556, 16.096]), healthy dietary patterns (HR: 0.677 [0.460, 0.995]), and tobacco exposure (HR: 0.508 [0.276, 0.935]) reduced mortality in patients with allergic comorbidities. These findings were consistent with single-variable models (Table A.3).

In the 6-state transitions (Figure A.2), variable associations aligned with the 4-state model. Notably, male sex increased AR risk; shorter

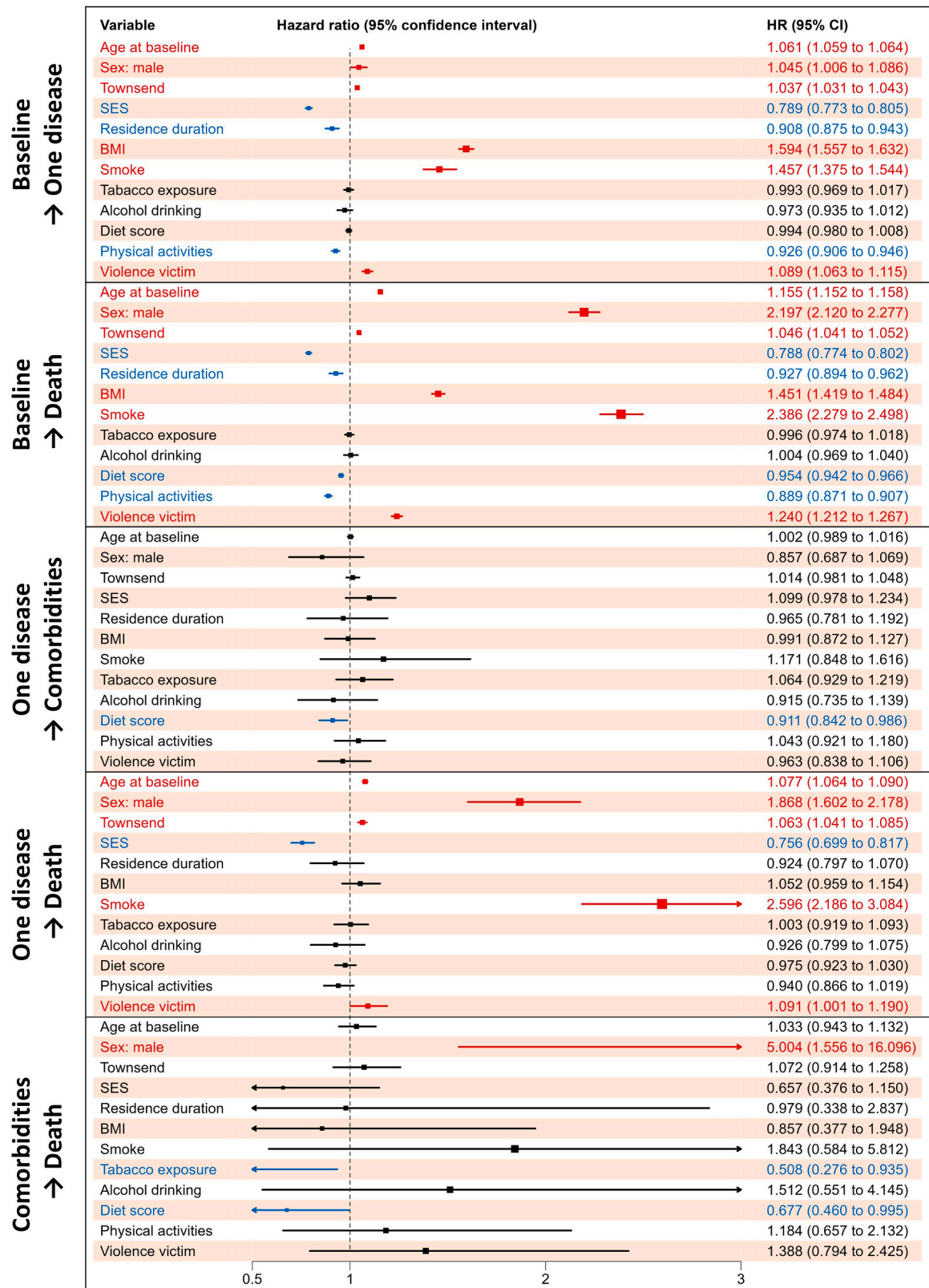


Fig. 4. Forest plots of HRs (95 % CIs) for each transition in 4-state transitions by demographic characteristics, social determinants and lifestyle factors.

residential duration, violent victimization, and unhealthy diet/exercise habits elevated asthma susceptibility. AD patients with alcohol consumption/unhealthy diets, smoking AR patients, and high-SES asthma patients had higher comorbidity rates. Higher SES reduced mortality risk in AR and asthma patients, while tobacco exposure increased

asthma-related mortality.

3.3. Air pollution and progression of allergic diseases

The 2010 annual mean concentrations of PM_{2.5} (9.99 µg/m³), PM₁₀

(16.24 $\mu\text{g}/\text{m}^3$), NO_2 (26.74 $\mu\text{g}/\text{m}^3$), and NO_x (44.04 $\mu\text{g}/\text{m}^3$) were derived from LUR models, representing baseline exposure estimates calibrated against monitoring station data. Across all 3 types of adjusted models in 4-state transitions, pollutants were consistently associated with transitions from health to single allergic disease (Table 2). Specifically, in Model 3, each 1 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ and NO_2 was associated with HRs of 1.090 [1.073, 1.108] and 1.009 [1.007, 1.011] for single allergic disease onset, corresponding to 9.0 % and 0.9 % elevated risks, respectively. Additionally, $\text{PM}_{2.5}$ (HR: 1.079 [1.063, 1.095]), NO_2 (HR: 1.007 [1.005, 1.009]), and NO_x (HR: 1.004 [1.003, 1.005]) were identified as risk factors for mortality in healthy individuals. NO_2 (HR: 1.009 [1.000, 1.018]) further increased mortality risk in allergic patients. In 6-state transitions, PM_{10} increased comorbidity risk in AR patients (Table A.4), while $\text{PM}_{2.5}$ and NO_2 were linked to mortality risk in asthma patients.

3.4. Prediction of allergic disease incidence and mortality

We validated the predictive utility of all listed risk factors through LASSO regression modeling for simultaneous prediction of allergic disease incidence and mortality. The training set AUC was 0.7856 (95 % CI: 0.7822–0.7890), and the validation set AUC was 0.7826 (95 % CI: 0.7757–0.7896) (Fig. 5). In the LASSO regression model, 8 predictors were identified: higher SES and physical activity were recognized as protectors of the occurrence of allergic diseases and death, while smoking, higher BMI, male sex, older age, violent victimization, and higher $\text{PM}_{2.5}$ exposure were risk factors.

3.5. Subgroup and sensitivity analyses

We also performed subgroup analyses by age and sex. Results revealed significant sex- $\text{PM}_{2.5}$ interactions (females more susceptible) and stronger NO_2 -disease associations in the elderly (Table A.5). Furthermore, interaction analyses identified significant effect modification of BMI, dietary patterns, physical activity, and SES on pollutant-related health impacts (Table A.6). Higher SES reduced allergic disease risk or mortality in healthy individuals, while unhealthy diets and obesity exacerbated allergic disease or mortality risk. This may be mediated through the SES-related capacity to reduce actual pollutant

exposure and healthy lifestyle-modulated biological responses. Sensitivity analysis using the imputed dataset ($n = 165,291$) confirmed consistent effects for most variables (e.g., TDI, BMI, smoking status) compared with results from the pre-imputation complete-case dataset (Figure A.3), suggesting the stability of the main results regarding demographic characteristics, social determinants, and lifestyle factors. For air pollutants, after the imputation, $\text{PM}_{2.5}$ -associated mortality risk in allergic patients became significant, while the NO_2 effects on disease onset or mortality risk in healthy individuals became non-significant (Table A.7, Figure A.4). These divergences in pollutant effects may be attributed to limitations in imputation accuracy. When including TDI in Model 3, $\text{PM}_{2.5}$ maintained significant hazard effects, while NO_2 exhibited paradoxical protective associations against all-cause mortality in healthy individuals (Table A.8, Figure A.5). The results showed that including TDI obscured the effect of pollutants on allergic disease incidence, as TDI demonstrated a strong correlation with NO_2 ($r = 0.48$, Figure A.6). Temporal sensitivity analysis showed that after follow-up truncation at 5 years, pollutant effect estimates were slightly attenuated, and NO_2 no longer exerted an effect on mortality risk in allergic patients. On the other hand, after excluding individuals with events occurring during the initial 5-year period, we observed two additional $\text{PM}_{2.5}$ -associated mortality risks in healthy individuals and allergic disease patients (Table A.9, Figure A.7–8). These findings implied that both $\text{PM}_{2.5}$ and NO_2 had cumulative long-term effects on the progression of allergic diseases.

4. Discussion

Based on the large prospective UKB cohort, we utilized multi-state models to investigate the impacts of social determinants, lifestyle factors, and air pollutants on allergic disease trajectory, from baseline health to incident allergic disease, comorbidities, and mortality. Our results demonstrate that adverse social determinants (lower SES, higher TDI, shorter residential duration, and violent victimization), unhealthy lifestyles (elevated BMI, smoking, physical inactivity), and higher air pollutant exposures ($\text{PM}_{2.5}$, NO_2) significantly increased allergic disease incidence. Furthermore, healthy dietary patterns attenuated progression to comorbidities, while lower SES, high TDI, violent victimization, smoking and NO_2 exposure heightened mortality risk in patients with

Table 2
HRs (95 % CIs) of Pollutants for each transition in 4-state transitions.

Pollutants (1 $\mu\text{g}/\text{m}^3$)	State	Model 1	Model 2	Model 3
		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
$\text{PM}_{2.5}$	Baseline $\rightarrow$ One allergic disease	1.077 (1.060,1.094)	1.124 (1.107,1.142)	1.090 (1.073,1.108)
	Baseline $\rightarrow$ Death	1.068 (1.053,1.084)	1.145 (1.129,1.161)	1.079 (1.063,1.095)
	One allergic disease $\rightarrow$ Allergic comorbidities	1.032 (0.944,1.128)	1.031 (0.940,1.131)	1.038 (0.946,1.138)
	One allergic disease $\rightarrow$ Death	1.083 (1.017,1.154)	1.134 (1.066,1.207)	1.047 (0.982,1.117)
	Allergic comorbidities $\rightarrow$ Death	1.038 (0.682,1.580)	1.155 (0.744,1.792)	1.143 (0.637,2.049)
PM_{10}	Baseline $\rightarrow$ One allergic disease	1.022 (1.013,1.031)	1.033 (1.024,1.042)	1.024 (1.015,1.033)
	Baseline $\rightarrow$ Death	1.003 (0.995,1.011)	1.022 (1.014,1.031)	1.005 (0.997,1.013)
	One allergic disease $\rightarrow$ Allergic comorbidities	1.052 (1.001,1.105)	1.053 (1.003,1.106)	1.037 (0.987,1.091)
	One allergic disease $\rightarrow$ Death	1.022 (0.987,1.059)	1.020 (0.985,1.056)	0.986 (0.951,1.022)
	Allergic comorbidities $\rightarrow$ Death	1.158 (0.950,1.412)	1.204 (0.990,1.465)	1.157 (0.893,1.499)
NO_2	Baseline $\rightarrow$ One allergic disease	1.006 (1.004,1.008)	1.013 (1.011,1.015)	1.009 (1.007,1.011)
	Baseline $\rightarrow$ Death	1.003 (1.001,1.005)	1.014 (1.012,1.016)	1.007 (1.005,1.009)
	One allergic disease $\rightarrow$ Allergic comorbidities	0.999 (0.986,1.011)	0.998 (0.985,1.011)	0.999 (0.986,1.013)
	One allergic disease $\rightarrow$ Death	1.009 (1.000,1.018)	1.015 (1.006,1.024)	1.009 (1.000,1.018)
	Allergic comorbidities $\rightarrow$ Death	0.979 (0.915,1.048)	0.984 (0.926,1.045)	0.986 (0.906,1.073)
NO_x	Baseline $\rightarrow$ One allergic disease	1.004 (1.003,1.005)	1.007 (1.006,1.008)	1.005 (1.004,1.006)
	Baseline $\rightarrow$ Death	1.003 (1.002,1.004)	1.007 (1.007,1.008)	1.004 (1.003,1.005)
	One allergic disease $\rightarrow$ Allergic comorbidities	1.000 (0.994,1.006)	1.000 (0.994,1.006)	1.000 (0.994,1.007)
	One allergic disease $\rightarrow$ Death	1.003 (0.999,1.008)	1.006 (1.002,1.010)	1.003 (0.999,1.007)
	Allergic comorbidities $\rightarrow$ Death	0.990 (0.959,1.023)	0.994 (0.967,1.022)	1.005 (0.964,1.048)

Model 1 solely incorporated each pollutant separately.

Model 2 adjusted for sex and age at baseline.

Model 3 adjusted for sex, age, socioeconomic status (SES), violence victim, residence duration, BMI, smoke status, tobacco exposure, diet score, alcohol drinking and physical activities.

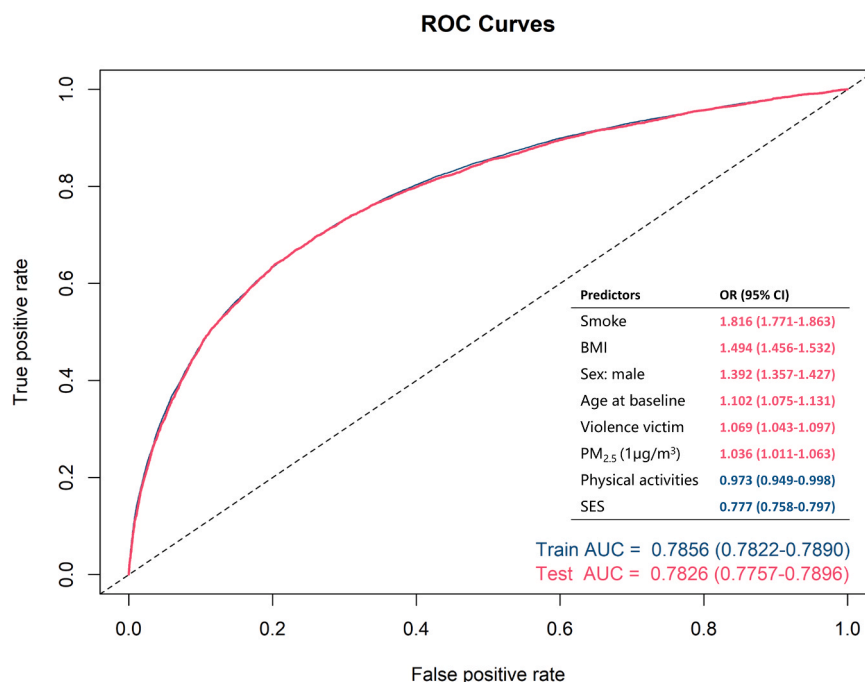


Fig. 5. ROC curves and odds ratio (ORs) of the predictors in the LASSO regression model for the incidence of allergic diseases and all-cause death.

single allergic conditions.

Our findings partially support that the incidence of allergic diseases in healthy adults was associated with multidimensional factors. For social determinants, higher individual-level SES and lower postcode-level TDI were associated with reduced allergic disease risk. This finding stands in partial contrast to previous systematic reviews (Uphoff et al., 2015). Prior investigations have reported that asthma onset is associated with lower SES, while the prevalence of other allergic diseases is linked to higher SES (Choi et al., 2021; Chong and Chew, 2018). As discussed in previous studies, the role of SES in allergy development remains unclear, and further studies are needed to clarify these inconsistent associations (Uphoff et al., 2015). Notably, violent victimization increased the risk of allergic diseases (HR = 1.089 [1.063, 1.115]), consistent with prior reports (OR = 1.52 [1.41, 1.64]) (Nash et al., 2023), potentially mediated by trauma-induced HPA axis dysfunction promoting chronic inflammation (Gaietto and Celedón, 2022; Wang, 2023). Additionally, longer residential duration demonstrated protective effects, possibly via microbial exposure immunotolerance or environmental desensitization (Schuijs et al., 2015). For lifestyle factors, established risk factors including elevated BMI and smoking were confirmed to elevate allergy risk in our cohort (Global Burden of Disease 2019; Cancer Collaboration et al., 2022; Maintz et al., 2023; Sio and Chew, 2021; Thomson, 2022). Regarding air pollutants, both our findings and prior epidemiological studies highlight PM_{2.5} and NO₂ as primary environmental drivers of allergic disease onset (Burte et al., 2018; Fadadu et al., 2023; He et al., 2024; Wang et al., 2020).

While current research predominantly focuses on the multifactorial determinants of allergic disease onset, their roles in shaping longitudinal comorbidity development and mortality trajectories across multiple allergic conditions remain understudied. Our multi-state analysis reveals that SES, TDI, violent victimization, smoking, and NO₂ exposure significantly accelerate the transition from single allergic disease to mortality, thereby demonstrating stage-specific risk amplification throughout the disease continuum—from incident disease to terminal outcomes. Notably, in patients with single allergies, SES, TDI, and smoking exhibited significantly higher adjusted HRs for mortality than in healthy individuals. This differential effect likely stems from chronic inflammatory priming and immune dysregulation in allergic patients,

wherein these factors accelerate pathological progression through potentiated oxidative stress and inflammatory cascades (e.g., SES/TDI increase environmental exposures while reducing healthcare access) (Munoz-Pizza et al., 2020; Pan et al., 2023; Zhang et al., 2025). Conversely, violent victimization and NO₂ exposure showed stronger mortality associations in healthy individuals relative to patients with single allergic conditions, possibly attenuated in allergy patients by proactive disease management (e.g., medication adherence, environmental avoidance) (Stefanovic et al., 2020). The underlying stage-dependent mechanisms still require further investigation for validation. Critically, our multi-state analysis revealed that healthy dietary patterns conferred dual protection: attenuating both progression to allergic comorbidities (HR = 0.911 [0.842, 0.986]) and mortality transitions from comorbid states (HR = 0.677 [0.460, 0.995]). This persistent safeguarding effect across disease evolution phases establishes diet as a critical safeguard throughout the disease continuum (Testa et al., 2020; Xu et al., 2023; Zhang, 2023). Additionally, in asthma patients, both PM_{2.5} (HR = 1.092 [1.015, 1.174]) and NO₂ (HR = 1.013 [1.003, 1.023]) increased mortality risk, with PM_{2.5} exerting a slightly stronger effect. This differential impact aligns with established evidence of PM_{2.5}'s heightened pulmonary toxicity, attributable to deeper alveolar penetration and amplified oxidative stress, which disproportionately exacerbates terminal outcomes in compromised airways of asthmatic patients (He et al., 2024; Zhu et al., 2024).

Additionally, in the transition from a single allergic disease to comorbidities, we observed that PM₁₀ exposure and low SES were significant risk factors. Mechanistically, PM₁₀'s coarse particles may exacerbate epithelial barrier dysfunction in AD/AR patients, promoting direct epithelial breach and subsequent immune activation, thereby accelerating comorbidities (Hassoun et al., 2019). While the role of SES in allergic diseases remains incompletely understood (Uphoff et al., 2015), our findings suggest its effects may vary by disease stage. Investigating a single outcome alone is insufficient to fully characterize this stage-dependent role, thus necessitating integration of dynamic disease progression for comprehensive assessment.

Subgroup analysis revealed that males exhibited higher allergic disease incidence, but reduced susceptibility to PM_{2.5}. This may reflect androgen-mediated immune suppression and/or adaptive tolerance

from chronic occupational PM_{2.5} exposure (Hassoun et al., 2019; Li et al., 2023). Older adults demonstrated heightened sensitivity to NO₂ in allergic disease onset, potentially attributable to age-related physiological decline in antioxidant defenses (Eguiluz-Gracia et al., 2020; Fadadu et al., 2023). Interaction analysis revealed that high SES buffered pollutant-induced mortality in healthy individuals, likely due to reduced actual exposure via socioeconomic-behavioral protective pathways (e.g., air purification measures and low-pollution commuting behaviors) among high-SES populations (Hajat et al., 2021; Munoz-Pizza et al., 2020). Conversely, high BMI exacerbated pollutant toxicity, possibly through compromised lung function, airway resistance, and obesity-related metabolic inflammation (Pekince Md and Baccioglu Md, 2022; Tiotiu et al., 2020).

Sensitivity analyses showed that most effect sizes remained stable after missing data imputation, supporting the robustness of results. However, the effects and significance of PM_{2.5} and NO₂ shifted, partially due to inherent challenges in the robustness of imputation methods: given the geographical dependence of pollutant concentrations, our lack of individual-level address data precluded incorporating spatial variables (e.g., proximity to traffic or industrial zones) into the imputation models, reducing the accuracy of imputed values. Consequently, the observed shifts in effect significance may reflect residual geographic bias rather than true biological associations. To address potential confounding between TDI and SES, both were included in sensitivity analyses (Model 3). Notably, NO₂ exhibited paradoxical protective associations with mortality in healthy participants when TDI was retained, likely due to spatial collinearity ($r > 0.20$ for all pollutants) between TDI and air pollutants, which obscured pollutant-outcome relationships and introduced residual confounding. Therefore, TDI was excluded from fully adjusted models while individual SES was retained as a socioeconomic variable. Sensitivity analysis with 5-year follow-up truncation and exclusion of participants with early events within 5-year follow-up suggested that most pollutants had cumulative long-term effects on the progression of allergic diseases rather than short-term exposure effects.

Our study identified social determinants, lifestyle factors, and air pollution as important modifiable factors associated with allergic disease trajectories. These observational associations support the development and validation of hierarchical prevention frameworks in future allergic disease research, including: primary prevention strategies targeting pollutant control and socioeconomic equity to reduce incidence; secondary prevention approaches combining high-risk surveillance with environmental protection to delay comorbidities; and tertiary prevention protocols investigating multicomponent interventions, which could combine psychosocial support, sustained smoking cessation programs, and precision anti-inflammatory nutrition, to mitigate disease-related disability and mortality in established cases. These evidence-informed hypotheses and frameworks require rigorous interventional validation before implementation.

Major strengths of our study include the large longitudinal UKB cohort, standardized data collection protocols, and comprehensive covariate data, which enabled the construction of multi-state models to characterize allergic disease transitions and robustly control for potential confounders. While Cox regression assesses single endpoint risks, it is structurally limited in parsing temporal dynamics of multiphase progression. The multi-state framework provides a distinct advantage by quantifying transition-specific risk across multidimensional factor profiles. This allowed us to identify sensitive stages of allergic disease onset, progression, and modulation by multidimensional factors.

Our study had several limitations. First, we could not assess other allergic diseases (e.g., food allergy) or outcome variables (e.g., allergic disease attack frequency and severity) due to the unavailability of data in the UKB. Second, pollutant data from 2010 were employed as a static proxy for baseline exposure, potentially introducing bias given the UK's pollution control policies over the past decade. UKB data lacked temporal resolution to capture exposure changes or lagged effects, limiting

the assessment of longitudinal exposure variation. Future studies should integrate dynamic exposure assessments to differentiate between short-term and long-term impacts of pollution on allergic disease.

5. Conclusion

In conclusion, based on a large-scale prospective adult cohort from the UKB, our study suggests that improving socioeconomic equity, promoting healthy lifestyles, and implementing targeted control measures for key air pollutants may reduce the risk of allergic disease onset, delay comorbidity progression, and mitigate related mortality. Future experimental research is required to systematically validate whether hierarchical prevention frameworks targeting these multidimensional factors across disease stages can effectively reduce population-level allergic morbidity and mortality.

Ethical Approval

There is no explanation of any issues relating to journal policies. All authors have read and approved this submission for publication. And there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript. The work is original and has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. I have obtained written permission from all persons named in the Acknowledgement.

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CRediT authorship contribution statement

Yinan He: Writing – review & editing, Writing – original draft, Validation. **Jialu He:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Dequan Shen:** Writing – review & editing, Writing – original draft, Validation. **Chengyin Ye:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jiahui Wu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Data curation. **Yuchang Xu:** Writing – review & editing. **Hanxin Lu:** Writing – review & editing, Writing – original draft, Investigation. **Weihong Tang:** Supervision, Project administration, Methodology, Formal analysis, Data curation. **Hui Huang:** Writing – review & editing.

Author contributions

CY and JH have made substantial contributions to conception and design of the study. CY and JH have made substantial contributions to acquisition of data. CY, JW, DS and JH have made substantial contributions to analysis and interpretation of data. DS, YH and WT have been involved in interpretation of data. CY and JW have made substantial contributions to draft the manuscript. DS, HL, YX and HH have been involved in drafting the manuscript. All authors revised the manuscript and gave final approval of the version to be published.

Declaration of Competing Interest

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2025.118806](https://doi.org/10.1016/j.ecoenv.2025.118806).

Data availability

Data will be made available on request.

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