Ambient air pollution and the dynamic transitions of stroke and dementia: a population-based cohort study

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Summary

Background Stroke and dementia are the leading causes of neurological disease burden. Detrimental effects of air pollution on both conditions are increasingly recognised, while the impacts on the dynamic transitions have not yet been explored, and whether critical time intervals exist is unknown.

Methods This prospective study was conducted based on the UK Biobank. Annual average air pollution concentrations at baseline year 2010 estimated by land-use regression models were used as a proxy for long-term air pollution exposure. Associations between multiple air pollutants ($PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_2) indicated by air pollution score and the dynamic transitions of stroke and dementia were estimated, and the impacts during critical time intervals were explored. The date cutoff of this study was February 29, 2020.

Findings During a median follow-up of 10.9 years in 413,372 participants, 6484, 3813, and 376 participants developed incident stroke, dementia, and comorbidity of stroke and dementia. For the overall transition from stroke to comorbid dementia, the hazard ratio (HR) for each interquartile range (IQR) increase in air pollution score was 1.38 (95% CI, 1.15, 1.65), and the risks were limited to two time intervals (within 1 year and over 5 years after stroke). As for the transition from dementia to comorbid stroke, increased risk was only observed during 2–3 years after dementia.

Interpretation Our findings suggested that air pollution played an important role in the dynamic transition of stroke and dementia even at concentrations below the current criteria. The findings provided new evidence for alleviating the disease burden of neurological disorders related to air pollution during critical time intervals.

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Keywords: Air pollution; Stroke; Dementia; Dynamic transitions; Critical time intervals

Introduction

With the rapid expansion of the aged population, the world has witnessed an increasing burden attributable to neurological disorders. Stroke and dementia are the leading causes of neurological death and disability worldwide.[1] Stroke, which accounts for 11.6% of total deaths globally, is the second-leading cause of death after ischemic heart disease.[2] In 2019, the number of people with dementia was over 50 million, and it is projected that the number will increase to 152 million by 2050.[3] Considering the fatal outcome of stroke and the limited interventions available to delay or prevent the onset of dementia, research on the modifiable risk factors of stroke and dementia remains a clinical and public health priority.

Stroke and dementia may pose reciprocal risks to each other. Stroke has been identified to be a risk factor for dementia, with the chance of developing dementia doubling among stroke patients.[4] In turn, dementia is suggested to be associated with an increased risk of stroke.[5] Not only do stroke and dementia share a number of modifiable risk factors, but they also share numerous pathophysiological mechanisms such as neuroinflammation, oxidative stress, blood–brain

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Research in context

Evidence before this study

The detriments of air pollution on stroke and dementia are increasingly recognised. We searched PubMed from database inception up to April 17, 2023 using the following search terms (title or abstract word): ("air pollution" OR "air pollutant" OR "particulate matter" OR "nitrogen dioxide" OR "nitrogen oxides") AND ("stroke" OR "dementia"). Several cohort studies have demonstrated that long-term air pollution exposure was associated with the increased risk of stroke or dementia, respectively. Nevertheless, the impact of air pollution in the dynamic transitions of stroke and dementia is unknown, and no study has investigated critical time intervals of air pollution for the transition of stroke and dementia.

Added value of this study

In this population-based cohort study, we found that long-term air pollution exposure was associated with dynamic transitions of stroke and dementia even at air pollution levels below the limits of EPA, UK and European Union. Furthermore, different critical time intervals for air pollution were observed in the dynamic transitions of stroke and dementia. To be specific, the adverse impacts of air pollution were observed within 1 year and over 5 years after stroke in the transition from stroke to comorbid dementia, while the detrimental influence was only observed during 2–3 years after dementia in the transition from dementia to comorbid stroke.

Implications of all the available evidence

Our findings suggested that air pollution may play an important role in the dynamic transitions of stroke and dementia even at concentrations below the current criteria. The findings of potential critical time intervals indicated the necessity of precise preventive strategies for air pollution. Given that many countries' air quality standards are still well above the latest World Health Organization Global Air Quality Guidelines 2021, stricter standards or regulations for air pollution control should be implemented in the future to alleviate the burden of neurological disorders.

barrier change, and disturbances of cerebrovascular hemodynamics.[6] Thus, participants with stroke were more likely to further develop comorbid dementia and vice versa, and it is reasonable to hypothesise the "transition" from incident stroke to comorbid dementia as well as from incident dementia to comorbid stroke. The investigation on the effect of risk factors in the "transition" would be important for prevention strategies.

Recently, the detrimental impacts of air pollution on neurological disorders have received increasing attention. Emerging evidence demonstrates that long-term exposure to ambient air pollution is a risk factor both for stroke and dementia.[7,8] In addition, the impacts of air pollution on stroke and dementia at air pollution concentrations below the current US Environmental Protection Agency (EPA) annual standard, the limits of the UK, and the European Union are attracting broad public attention. However, previous studies only concentrated on the influence of air pollution on stroke or dementia. It remained unknown whether ambient air pollution was associated with the dynamic transitions of stroke and dementia, such as from baseline to stroke/dementia, further to comorbidity of stroke and dementia, and subsequently to death, especially at low air pollution levels.

Furthermore, epidemiological studies have indicated that the duration of disease would influence the incident risk of its comorbidities,[9,10] and emerging evidence suggested that the risk from stroke or dementia to comorbidity varied during different time intervals.[11] Therefore, we hypothesised that the impacts of ambient air pollution on the transitions from stroke or dementia to their comorbidity may also vary over different time intervals, and potential critical time interval may exist, which would provide novel evidence for the influence of air pollutants in a finer time scale, and contribute to optimising prevention and management strategies of stroke or dementia. However, the critical time intervals of air pollution on stroke and dementia have not been investigated as yet.

In addition, ambient air pollution is a mixture of both particulate matter and gaseous pollutants, and evaluating the health effects of multiple air pollutants as a whole has been increasingly recognised. Drawing upon UK Biobank, we assessed the impacts of joint exposure to multiple air pollutants on the dynamic transitions of stroke and dementia, especially focusing on the influence of air pollution during different time intervals.

Methods

Study design and population

The UK Biobank is a large, population-based prospective study. During 2006 to 2010, over 500,000 participants aged 40–69 years were recruited and sociodemographic information, lifestyles, and health information were collected at baseline. The date cutoff of this study was February 29, 2020.

We identified stroke and dementia cases at baseline and during follow-up according to algorithmically-defined outcomes in the UK Biobank. Among the 502,412 participants recruited at baseline, those who reported prevalent stroke, dementia, or cancer were excluded. Participants with missing data on air pollution

exposure or covariates were also excluded. Participants diagnosed with stroke and dementia on the same date were further excluded since the chronological order of disease development was unclear.

Ethics

All the participants in the UK Biobank provided written consent and UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (21/NW/0157). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Air pollution assessment

Annual estimates of air pollutants including particulate matter (PM) with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), PM with aerodynamic diameter between 2.5 μm and 10 μm ($PM_{2.5\text{-}10}$), and nitrogen dioxide (NO_2) were modelled based on each participant's residential address using a land use regression model (LUR) as a part of the European Study of Cohorts for Air Pollution Effects (ESCAPE). To be specific, air pollution was measured with passive samplers in the study area. $PM_{2.5}$ and PM_{10} were sampled using Harvard Impactors, and the coarse fraction (PM_{coarse}) was calculated as the difference between PM_{10} and $PM_{2.5}$.[12] NO_2 was measured with Ogawa passive samplers.[13] The measured average concentrations were combined with centrally and locally available Geographic Information System (GIS)-derived predictor variables such as traffic intensity, population density, and land-use to develop LUR models.[12,13] Ambient air pollution concentrations of the participants were then assigned according to their residential coordinates in the 100 m × 100 m grid cells.[14] The LUR models explained a large fraction of the spatial variance in air pollutants with median model variance (R^2) being 71% for $PM_{2.5}$, 68% for $PM_{2.5\text{-}10}$, and 82% for NO_2, respectively. Since only baseline air pollution information was available in the UK Biobank, annual average air pollution concentration of the year 2010 was used as a proxy for long-term air pollution exposure as previous studies.[14–16] An air pollution score incorporating the abovementioned air pollutants was created with principal components analysis (PCA). The first principal component which contributed to the main proportion of the total variance was named as air pollution score.[17]

Follow-up and outcome ascertainment

All the participants were followed up from the date of recruitment to death, loss to follow-up, or February 29, 2020, whichever came first. Incidence of stroke and dementia were ascertained from algorithmically-defined outcomes in the UK Biobank, which incorporated information from UK Biobank's baseline assessment (prevalent cases that occurred before recruitment), along with linked data from hospital admissions and death registries. Code lists for stroke and dementia were detailed in eMethods in Supplement Material. Comorbidity was defined as diagnoses with stroke or dementia at first and further the other. Incident cases of death were obtained through linkage to national death registries.

Covariates

A directed acyclic graph including a variety of demographic factors, socioeconomic status as well as lifestyles was developed to identify potential confounders. A minimally sufficient adjustment set (age, sex, ethnicity, education level, Townsend deprivation index, and assessment centre) was identified to be potential confounders and adjusted in the main models (Fig. S1). In the sensitivity analysis, lifestyles including smoking status, alcohol frequency, physical activity, and healthy diet score were further adjusted. The information on covariates was detailed in eMethods in Supplement Material.

Statistical analysis

First, we used traditional Cox proportional hazard models with time-on-study as timescale and not considering delayed entry to assess the associations of air pollution with incident stroke, incident dementia, comorbidity of stroke and dementia, and all-cause mortality. Survival time for each participant was calculated as the duration from the date of recruitment through the time of death, loss to follow-up, or February 29, 2020. Death was considered as censored. No violation of the assumption of proportional hazard was detected through Schoenfeld residual testing (Fig. S2). The Fine and Gray model was also used to assess the associations of air pollution with incident stroke, incident dementia, and comorbidity of stroke and dementia considering the potential competing risk of death from other causes. In trajectory analyses, multi-state models were used to assess the associations of air pollution with the dynamic transitions of stroke and dementia. Multi-state model is an extension of traditional Cox proportional hazards model by incorporating multiple subsequent or competing events as states of transitions to assess the influence of risk factors on different stages of disease progression simultaneously. The multi-state model in our study consisted of five states including baseline, stroke, dementia, comorbidity of stroke and dementia, and all-cause mortality. Accordingly, eight transitions between five states were considered: 1) from baseline to stroke, 2) from stroke to comorbid dementia, 3) from baseline to dementia, 4) from dementia to comorbid stroke, 5) from baseline to death, 6) from stroke to death, 7) from dementia to death, 8) from comorbidity to death. For the participants with the same date for disease and death, the entering date of disease was set as the initial date minus 0.5 day according to previous studies.[15] The results were presented as hazard

ratios (HRs) with 95% confidence intervals (CIs) for each interquartile range (IQR) increase in air pollution score as well as individual air pollutants. The IQR values for $PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_2 were 1.27 μg/m^3, 0.79 μg/m^3, and 9.85 μg/m^3, respectively. The exposure–response relationships of air pollution with the transition from stroke to comorbidity and the transition from dementia to comorbidity were depicted using restricted cubic spline functions for continuous air pollution variables with 3 knots. The Akaike information criterion (AIC) was applied to choose the number of knots of restricted cubic spine, between 3 and 7. If the number of knots with least AIC was observed differently between the two transitions, the lower number would be chosen for a balance between best fit and overfitting.[18] The widely used locations of knots was applied: the 10th, 50th, and 90th percentile of exposure level.[19]

To assess the risks of air pollution during different time intervals within the transitions from stroke or dementia to comorbidity, we applied a piecewise Cox model and segmented the periods after the incident stroke or dementia to comorbidity (0–1 year, 1–2 year, 2–3 year, 3–4 year, 4–5 year, >5 years). The piecewise Cox model was used to analyse survival outcomes in the full cohort, with results reported as separate hazard ratios for time segments.[20] The impacts of air pollution in each time segment within the transitions from stroke or dementia to comorbidity were evaluated to explore potential critical time intervals.

The associations between air pollution and transitions from stroke or dementia to comorbidity were further stratified according to age (<65 versus ≥65 years), sex (female versus male), Townsend deprivation index (<median versus ≥ median), and education level (university or college degree versus others). The modification effect was tested with likelihood-ratio tests by comparing models with and without a cross–product interaction term of air pollution and the stratified factor.

Several sensitivity analyses were conducted to assess the robustness of the associations of air pollution with dynamic transitions of stroke and dementia. (1) Participants younger than 50 years old were excluded considering stroke and dementia generally occur in older adults. (2) Stroke and dementia cases diagnosed in the first year of follow-up were excluded to partly avoid the possible influence of the existing disease condition according to previous studies.[21] (3) Several lifestyle factors including smoking status, frequency of alcohol intake, physical activity, and healthy diet scores were additionally adjusted to be in keeping with priori knowledges and previous studies which explored the influence of air pollution on stroke or dementia.[22,23] (4) For the participants who were diagnosed with a disease and died on the same date, the entry date of disease was set as the initial date minus the median transition time (eMethods in Supplement Material). (5) The participants with the diagnoses of stroke and dementia on the same date were included and a transition from baseline to comorbidity in the transition pattern was added. (6) An air pollution score including all the four air pollutants ($PM_{2.5}$, $PM_{2.5\text{-}10}$, NO_2, and NO) was calculated to justify the robustness of our results. (7) A sensitivity analysis was conducted by considering how long the participants have lived at the same address. (8) The diagnosis of stroke and dementia from first occurrence which involves data from primary care in the UK Biobank was used. (9) Participants with cancer at baseline were further included. (10) Participants with "blue collar" history were excluded to avoid the influence of occupational exposure. (11) Multiple imputation using chained equations by exposures and covariates was conducted considering the protential bias of missing data. (12) Time-varying $PM_{2.5}$ was used to address the rationality of using annual air pollution concentrations at baseline year 2010 as a proxy for long-term air pollution exposure.

All statistical analyses were conducted with R software (version 4.2.2) and the multi-state models were performed with the "mstate" package.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All the authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

A total of 413,372 participants were included in main analysis (Fig. S3), among which 224,251 (54.2%) were female, and the mean (SD) age was 56.2 (8.1) years. The mean (SD) concentrations (μg/m^3) of $PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_2, were 10.0 (1.1), 6.4 (0.9), and 26.6 (7.6), respectively (Table 1). During a median follow-up of 10.9 (10.3–11.6) years, 6484 (1.6%, 1.5/1000 person-years) and 3813 (0.9%, 0.9/1000 person-years) participants were diagnosed with stroke or dementia, respectively. In addition, 238 (3.7%, 10.4/1000 person-years) participants with stroke were further diagnosed with dementia, and 138 (3.6%, 17.4/1000 person-years) participants with dementia were further diagnosed with stroke (Fig. 1).

Assessing by traditional Cox proportional hazard models and the competing risk models, significantly positive associations of air pollution with incident dementia, comorbidity of stroke and dementia, and all-cause mortality were observed (Tables S3 and S4). Furthermore, the multi-state models showed that air pollutants were associated with dynamic transitions of stroke and dementia (Table S5). For each IQR increase in $PM_{2.5}$, the HRs were 1.08 (95% CI, 1.03, 1.13; $P = 0.001$), 1.32 (95% CI, 1.11, 1.57; $P = 0.002$), and 1.07 (95% CI, 1.04, 1.09; $P < 0.001$) for the transition from

Characteristics	Total	Free of stroke/dementia	Incident stroke/dementia	Incident stroke & dementia
Number of participants (n)	413,372	403,075	9921	376
Age (years), mean ± SD	56.2 ± 8.1	56.1 ± 8.1	62.0 ± 6.4	64.8 ± 4.4
Sex				
Female	224,251 (54.2%)	219,725 (54.5%)	4382 (44.2%)	144 (38.3%)
Male	189,121 (45.8%)	183,350 (45.5%)	5539 (55.8%)	232 (61.7%)
Education				
University or college degree	134,059 (32.4%)	131,732 (32.7%)	2272 (22.9%)	55 (14.6%)
Other	279,313 (67.6%)	271,343 (67.3%)	7649 (77.1%)	321 (85.4%)
Ethnicity				
White	389,812 (94.3%)	379,994 (94.3%)	9466 (95.4%)	352 (93.6%)
Other	23,560 (5.7%)	23,081 (5.7%)	455 (4.6%)	24 (6.4%)
Townsend deprivation index				
Quintile 1 (least deprived)	82,624 (20.0%)	80,795 (20.0%)	1777 (17.9%)	52 (13.8%)
Quintile 2	82,724 (20.0%)	80,766 (20.0%)	1873 (18.9%)	85 (22.6%)
Quintile 3	82,658 (20.0%)	80,650 (20.0%)	1944 (19.6%)	64 (17.0%)
Quintile 4	82,688 (20.0%)	80,672 (20.0%)	1939 (19.5%)	77 (20.5%)
Quintile 5 (most deprived)	82,678 (20.0%)	80,192 (19.9%)	2388 (24.1%)	98 (26.1%)
$PM_{2.5}$ ($\mu g/m^3$), mean ± SD	10.0 ± 1.1	10.0 ± 1.1	10.0 ± 1.1	10.2 ± 1.1
$PM_{2.5-10}$ ($\mu g/m^3$), mean ± SD	6.4 ± 0.9	6.4 ± 0.9	6.4 ± 0.9	6.4 ± 0.9
NO_2 ($\mu g/m^3$), mean ± SD	26.6 ± 7.6	26.6 ± 7.6	26.9 ± 7.4	28.0 ± 8.0
Smoking				
Current or previous smoker	184,643 (44.8%)	179,103 (44.6%)	5303 (53.8%)	237 (63.5%)
Non-smoker	227,311 (55.2%)	222,618 (55.4%)	4557 (46.2%)	136 (36.5%)
Alcohol consumption				
<Once a week	125,524 (30.4%)	121,935 (30.3%)	3442 (34.7%)	147 (39.2%)
≥Once a week	202,613 (49.1%)	198,166 (49.2%)	4298 (43.4%)	149 (39.7%)
Daily or almost daily	84,905 (20.6%)	82,660 (20.5%)	2166 (21.9%)	79 (21.1%)
Air pollution score, mean ± SD	0.00 ± 1.40	0.00 ± 1.40	0.06 ± 1.38	0.25 ± 1.48

Air pollution score was calculated by $PM_{2.5}$, $PM_{2.5-10}$, and NO_2. SD: standard deviation, $PM_{2.5}$: particulate matter with aerodynamic diameter of 2.5 μm or less, $PM_{2.5-10}$: particulate matter with aerodynamic diameter between 2.5 μm and 10 μm, NO_2: nitrogen dioxide.

Table 1: **Descriptive characteristics of the study population.**

baseline to dementia, from stroke to comorbid dementia, and from baseline to death, respectively. Similarly, the HRs were 1.10 (95% CI, 1.04, 1.15; $P < 0.001$), 1.43 (95% CI, 1.16, 1.77; $P = 0.001$), and 1.08 (95% CI, 1.06, 1.11; $P < 0.001$) for the abovementioned three transitions for each IQR increase in NO_2. However, no significant association was observed between $PM_{2.5-10}$ and any transition. For each IQR increase in air pollution score, the HRs for the transitions from baseline to dementia, stroke to comorbid dementia, baseline to death were 1.07 (95% CI, 1.03, 1.12; $P = 0.002$), 1.38 (95% CI, 1.15, 1.65; $P = 0.001$), and 1.07 (95% CI, 1.05,

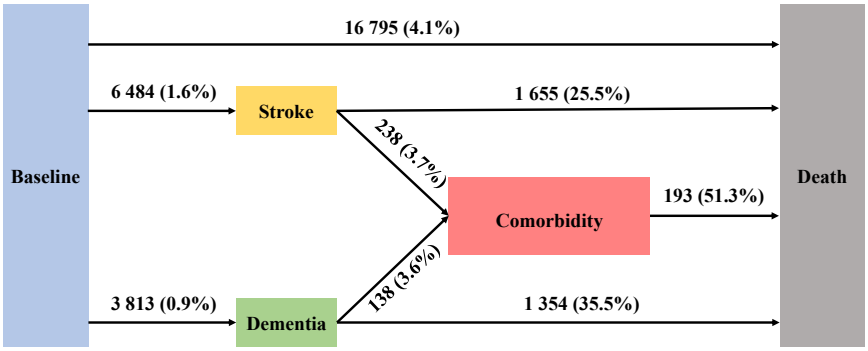

Fig. 1: Numbers (percentages) of participants in eight transition stages. The different coloured boxes represent the five states in the dynamic transitions of stroke and dementia. The arrows represent the transitions from one state to another.

1.09; $P < 0.001$), respectively (Table 2). The exposure-response curves for the association between air pollution score and the transitions of stroke and dementia were depicted in Fig. 2, and the curves for the individual air pollutant were depicted in Fig. S4. Linear trends for the transition from stroke to comorbidity associated with air pollution score, $PM_{2.5}$, and NO_2, were observed. Flat patterns for the transition from dementia to comorbidity associated with air pollution score and individual air pollutants were shown.

The risks of air pollution during different time intervals are shown in Fig. 3. The risk of air pollution for the transition from stroke to comorbid dementia was observed within 1 year and over 5 years after stroke, with the HR of 1.61 (95% CI, 1.12–2.32; $P = 0.011$) and 1.82 (95% CI, 1.31–2.52; $P < 0.001$) for each IQR increase in the air pollution score. No significant association was observed for the overall transition from dementia to comorbid stroke, while increased risk was only observed during 2–3 years after dementia, with the HR of 1.75 (95% CI, 1.06–2.90; $P = 0.029$) for each IQR increase in air pollution score.

We did not observe significant effect modification of age, sex, Townsend deprivation index, or education level for the association between air pollution and transitions from stroke or dementia to comorbidity (Table S6).

The associations of air pollution score with dynamic transitions of stroke and dementia in sensitivity analyses were robust (Tables S7–S20 and Figs. S5–S17).

Discussion

Based on this large, population-based prospective cohort, we found that air pollution played an important role in the dynamic transitions of stroke and dementia, even with air pollutants below the current EPA annual standards ($PM_{2.5}$: 12 μg/m^3, NO_2: 53 ppb), and the limits of the UK ($PM_{2.5}$: 20 μg/m^3, NO_2: 40 μg/m^3) as well as the European Union ($PM_{2.5}$: 25 μg/m^3, NO_2: 40 μg/m^3) standards. Air pollution was found to be associated with the transition from stroke to comorbid dementia, with the increased risks within 1 year and over 5 years after stroke. The adverse impact was observed during 2–3 years from dementia to comorbid stroke, albeit no obvious association with air pollution was observed for the overall transition from dementia to comorbid stroke.

To the best of our knowledge, this is the first time that the health impacts of air pollution on the dynamic transitions of stroke and dementia have been explored. The health impacts of air pollution on some specific transitions in the dynamic transition of stroke and dementia were consistent with previous studies which concentrated on single disease stages. For example, a meta-analysis involving 17 population-based cohort studies suggested that per 1 μg/m^3 increment in $PM_{2.5}$ was associated with a higher risk of dementia with the HR of 1.03 (95% CI, 1.02–1.05).[24] A national cohort study in the United States showed that for each IQR increase in $PM_{2.5}$ (3.2 μg/m^3) and NO_2 (11.6 ppb), the HRs were 1.060 (95% CI, 1.054–1.066) and 1.019 (95% CI, 1.012–1.026) for incident dementia, respectively.[25] However, such studies did not assess the health impacts of air pollution in the dynamic transitions of stroke and dementia such as the association between air pollution and the transition from stroke to comorbid dementia. Additionally, air pollution has been identified as a risk factor for mortality. A cohort study including all Medicare beneficiaries in the continental United States indicated that increase of 10 μg/m^3 $PM_{2.5}$ was associated with an increase in all-cause mortality of 7.3% (95% CI: 7.1%–7.5%).[26] A pooled analysis of eight European cohorts demonstrated that an increase of 5 μg/m^3 in $PM_{2.5}$ was associated with 13% (95% CI: 10.6%–15.5%) increase in natural deaths; the corresponding association for a 10 μg/m^3 increase in NO_2 was 8.6% (95% CI: 7%–10.2%).[27]

Transition	Case (Rate)	HR (95% CI)	*P* value
Baseline→Stroke/Dementia			
Baseline→Stroke	6484 (1.5)	1.03 (0.99, 1.06)	0.146
Baseline→Dementia	3813 (0.9)	1.07 (1.03, 1.12)	0.002
Stroke/Dementia→Comorbidity			
Stroke→Comorbidity	238 (10.4)	1.38 (1.15, 1.65)	0.001
Dementia→Comorbidity	138 (17.4)	1.08 (0.84, 1.39)	0.560
Other status→Death			
Baseline→Death	16,795 (3.8)	1.07 (1.05, 1.09)	<0.001
Stroke→Death	1655 (72.3)	0.98 (0.91, 1.05)	0.543
Dementia→Death	1354 (170.3)	1.00 (0.92, 1.09)	0.956
Comorbidity→Death	193 (366.5)	1.07 (0.83, 1.36)	0.613

Comorbidity means the comorbidity of stroke and dementia. Rate means cases per 1000 person-years. HR: hazard ratio, CI: confidence interval, IQR: interquartile range. The models were adjusted for age, sex, ethnicity, education, Townsend deprivation index, and assessment centre. HRs and 95% CI for each IQR increase in air pollution score were presented.

Table 2: **Associations between air pollution score and the dynamic transitions of stroke and dementia.**

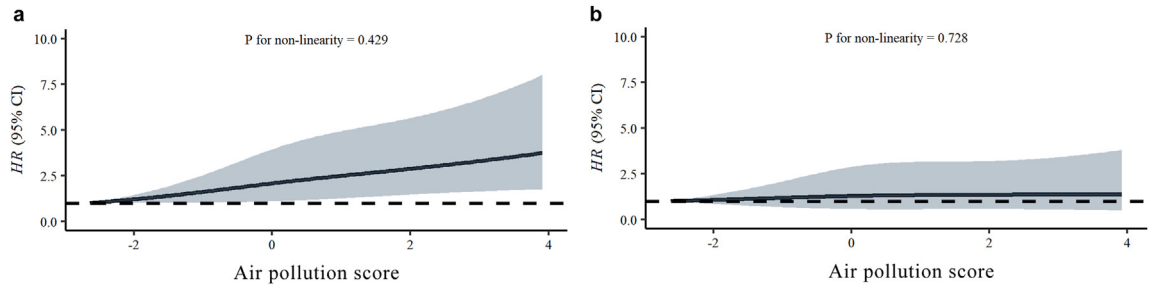

Fig. 2: Exposure-response curves of air pollution score with the transition from stroke to comorbidity (a) and the transition from dementia to comorbidity (b). The models were adjusted for age, sex, ethnicity, education, Townsend deprivation index, and assessment centre. Air pollution score levels range from the 0 to 99th percentiles. HR, hazard ratio; CI, confidence interval. The solid black lines are the HRs, and the grey areas are the 95% CIs.

Epidemiological studies have indicated that the duration of disease would influence the incident risk of its comorbidities,[10,28] and emerging evidence suggested that the risk from stroke or dementia to comorbidity varied during different time intervals.[11] Thus, the impacts of air pollution on the transitions from stroke/dementia to their comorbidity may also differ over different time intervals. Several studies have indicated the susceptible window for environmental factors on adverse pregnancy outcomes.[29,30] However, no study has assessed the critical time intervals on the transitions from stroke/dementia to their comorbidity associated with air pollution. By using piecewise Cox model which can analyse HRs over different time segments,[9] we have verified our hypothesis in this study. The discrepancy in the risk during different time intervals may reflect the varied patterns of air pollution on the two neurological disorders.

Stroke is an acute episode of focal dysfunction of the brain,[31] while dementia has usually a chronic or progressive nature.[32] Stroke may increase the risk of dementia shortly after the stroke episode, which is called early-onset poststroke dementia (PSD), but patients surviving stroke without early-onset PSD are at risk of developing delayed-onset PSD over the long term.[33] Acute stroke events would accelerate neuronal injury and neurodegeneration through diminished clearance and increased production of Aβ. Furthermore, acute inflammation, neurotoxicity, and metabolic disarray following the acute stroke would lead to contribute to dementia risk shortly after stroke (early-onset PSD).[34] While delayed-onset PSD may be driven mostly by sporadic small vessel disease (SVD).[35] Vulnerable periods both shortly after stroke and in the long term are warned due to the different mechanisms underlying early-onset and delayed-onset PSD, which may account

Transition	Time interval	Case (Rate)	P value	HR (95% CI)
Stroke→Comorbidity	0 to 1 years	47 (9.4)	0.011	1.61 (1.12, 2.32)
	1 to 2 years	33 (8.1)	0.437	1.21 (0.75, 1.94)
	2 to 3 years	40 (11.7)	0.867	1.04 (0.67, 1.61)
	3 to 4 years	26 (9.1)	0.249	1.35 (0.81, 2.24)
	4 to 5 years	24 (10.4)	0.583	0.84 (0.45, 1.58)
	>5 years	68 (12.9)	<0.001	1.82 (1.31, 2.52)
Dementia→Comorbidity	0 to 1 years	66 (23.2)	0.493	0.87 (0.59, 1.29)
	1 to 2 years	27 (14.3)	0.105	1.44 (0.93, 2.23)
	2 to 3 years	18 (14.6)	0.029	1.75 (1.06, 2.90)
	3 to 4 years	10 (12.5)	0.152	0.39 (0.11, 1.41)
	4 to 5 years	9 (17.7)	0.145	0.42 (0.13, 1.35)
	>5 years	8 (11.9)	0.583	1.32 (0.49, 3.56)

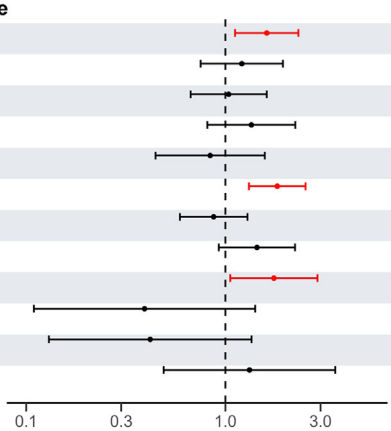

Fig. 3: Associations between air pollution score and dynamic transitions of stroke and dementia during different time intervals. Comorbidity means the comorbidity of stroke and dementia. Rate means cases per 1000 person-years. HR: hazard ratio, CI: confidence interval, IQR: interquartile range. The models were adjusted for age, sex, ethnicity, education, Townsend deprivation index, and assessment centre. HRs and 95% CI for each IQR increase in air pollution score were presented. The dots are the HRs, and the error bars are the 95% CIs. The dots and error bars coloured by red represent $P < 0.05$.

for the significant associations observed between air pollution and PSD both in short duration and in long term after stroke.

Participants with dementia tend to have cerebra amyloid angiopathy, microbleeds, and white-matter hyperintensities, which may in turn increase the risk of comorbid stroke.[5,36] When the deteriorating conditions in the CNS in the progression of dementia reach to a certain extent, air pollution may trigger the onset of stroke. Nevertheless, in contrast to the transition from stroke to comorbid dementia, no significant association of air pollution was observed for the overall transition from dementia to comorbid stroke. A systematic review and meta-analysis indicated that the impact of stroke on future dementia seems greater than the impact of cognitive impairment on future stroke.[36] This phenomenon might explain the null influence of air pollution on the overall transition from dementia to comorbid stroke to some extent. However, when considering the time intervals after incident dementia, increased risk of comorbid stroke associated with air pollution during 2–3 years after dementia was observed. The findings demonstrated that the impacts of air pollution on the transition from dementia to comorbid stroke during various time intervals exhibited different patterns. Thus, identifying the associations of air pollution with dementia and comorbid stroke in a finer time scale would contribute to optimising prevention and management strategies of them. Further researches into pathophysiological mechanisms underlying the associations during different time intervals are warranted.

There are several strengths in this study. The major strength is that a trajectory analysis was performed to assess the associations between air pollution and dynamic transitions of stroke and dementia using multistate models. Furthermore, whether the impact of air pollution varied during different time intervals was evaluated, which would identify potential critical time intervals for air pollution, as well as highlighting possible precise preventions. Additionally, UK is a useful proxy for air pollution with rural areas and areas of major congestion, and an air pollution score was created to characterise the joint exposure to air pollution, which would add importance to evaluating the integrated health impact of multiple air pollutants. Finally, the impacts of air pollution on the trajectory of neurological disorders were observed even at low levels, which may have important implications for policy making in future air pollution control.

Some limitations should also be noted. First, only baseline air pollution information was available in the UK Biobank, and annual average concentrations of the year 2010 was used to represent the long-term exposure to air pollution. However, air pollution emissions remained relatively stable from 2010 to 2019 in the UK,[37] and there is evidence showing that using annual mean air pollutants at baseline showed similar associations with that using time-varying air pollutants,[38,39] which is consistent with our sensitivity analysis. Second, occupational exposure and indoor exposure are additional potential confounders, but the air pollutants' concentrations in occupational and indoor places were not available in the UK Biobank, which would result in potential residual confounding. Third, considering that the sole use of hospital admission data for incident cases of dementia may lead to an underestimation of dementia cases, we conducted a sensitivity analysis to further include GP data and the results were robust. Fourth, the occurring order of stroke and dementia for the participants with the two diagnoses on the same date could not be confirmed and these participants were excluded in the main multi-state analysis. However, sensitivity analysis by including these participants and adding a transition from baseline to comorbidity was robust. Fifth, an interval of 0.5 day was used to calculate the entry date of disease if participants diagnosed with a disease died on the same date, which may affect the accuracy of the associations. Nevertheless, sensitivity analysis using the median interval time of transitions yielded similar results. Sixth, some of the results were based on a small proportion of all cases and large-scale studies should be conducted in the future to verify the findings. Seventh, a caveat should be kept in mind that the results should be generalized to places with different cooking sources with caution. Finally, the generalisation of the results to other populations should be cautious since a majority of participants in the UK Biobank are of European descent.

In this large, population-based cohort study, we found that long-term air pollution exposure played a detrimental role in the dynamic transitions of stroke and dementia even at low air pollution levels. Furthermore, the findings provide novel evidence for reducing the risk of neurological disorders related to air pollution during critical time intervals. Considering that many countries' air quality standards are still well above the latest World Health Organization Global Air Quality Guidelines 2021, stricter standards or regulations for air pollution control should be implemented in the future policy making to alleviate the burden of neurological disorders. Further investigation into pathophysiological mechanisms underlying these associations is warranted.

Contributors

JH (Jing Huang) and GL designed the study protocol and provided overall guidance. JH (Jing Huang) and GL had verified the underlying data. JW is responsible for conceptualisation, validation and writing-original draft. XH is responsible for data curation, formal analysis and validation. TY and JJ are responsible for methodology and software. JH (Junwei Hao) is responsible for writing-review & editing. FK contributed to guidance and writing-review & editing. All the authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Data sharing statement

The datasets used in this study are available in the UK Biobank repository (https://www.ukbiobank.ac.uk/).

Declaration of interests
None reported.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102368.

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