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Residential greenness, air pollution, and epilepsy: Insight in genetic susceptibility and life expectancy

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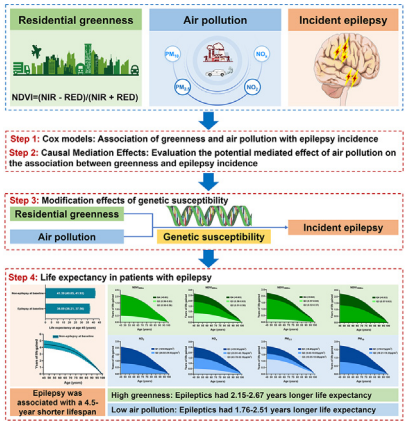
HIGHLIGHTS

- Greenness and air pollutants exposures were associated with epilepsy risk.
- There were significant interactions between greenness and genetic susceptibility.
- $PM_{2.5}$ mediated 38.26% to 48.38% of greenness associated with epilepsy.
- High greenness or low air pollutants may increase life expectancy in epileptics.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Epilepsy is one of the most common neurological disorders worldwide, yet evidence on its environmental determinants remains limited. Although a few studies have linked air pollution to epilepsy onset, the potential influence of residential greenness has not been investigated. Moreover, whether genetic susceptibility modifies these associations remains unclear.
Objectives: We aimed to examine the associations of residential greenness and air pollutants with incident epilepsy and to evaluate the modification effect of genetic susceptibility. We also assessed the relationship between environmental factors and life expectancy among people with epilepsy.
Methods: Residential greenness was quantified using the normalized difference vegetation index (NDVI) for 437,526 UK Biobank participants. Air pollution levels were estimated using land-use regression models. Polygenic risk scores (PRS) were calculated to assess genetic susceptibility to epilepsy. These relationships were examined using Cox models. Causal mediation analysis was employed to estimate the mediation effects. Furthermore, we calculated population attributable risk (PAR%) and life expectancy.
Results: Over a median follow-up of 11.78 years, 2,448 incident epilepsy were identified. Each interquartile-range increase in greenness was associated with a 7–8% lower risk of epilepsy, whereas

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air pollution was associated with a 5–9% higher risk. Additive and multiplicative interactions were observed between greenness and PRS (all SIs < 1; $P_{interaction}$ < 0.1), but not for air pollutants. PAR% for greenness and air pollutants ranged from 16.1% to 24.3%. $PM_{2.5}$ mediated 38.26–48.38% of the association between greenness and epilepsy. Epileptics exposed to high greenness or low air pollution had 1.76–2.67 years longer life expectancy at age 45. Given the observational design, further studies are warranted to confirm these findings.

Conclusions: Residential greenness and air pollutants were associated with epilepsy incidence and progression. Interactions between greenness and genetic susceptibility were observed. Mitigating air pollution and enhancing greenness may provide substantial neurological health benefits.

Introduction

Epilepsy ranks among the most prevalent neurological conditions globally, marked by abnormal discharge of the brain leading to seizures or functional impairments, including changes in behavior, sensations, and awareness [1]. Approximately 50 million individuals worldwide suffer from active epilepsy, exhibiting an incidence rate of 48.86 per 100,000 person-years in high-income countries [2]. In 2017, the European region recorded a cumulative total of 0.78 million disability-adjusted life-years due to epilepsy, alongside a 53% rise in epilepsy-related fatalities compared to 1990 [3]. Due to the heavy financial burden [4], epilepsy has become a public health imperative. Except for common etiology, more than 40% of epilepsy cases in adults are unknown [5]. Therefore, identifying modifiable factors and improving the lives of epileptics are high priorities to reduce disease burden.

Increasing evidence indicates that air pollution could be a contributing factor to epilepsy by influencing neuronal metabolism and excitability [6]. Numerous epidemiological studies have documented the short-term impacts of air pollutants on seizures, calls for medical emergencies, outpatient visits, and hospitalizations related to epilepsy [7–12]. To date, few studies have explored the association between long-term exposure to air pollution status and the incidence of epilepsy [13–15]. Recently, greenness has been linked to multiple human health benefits, which encompass lower rates of all-cause mortality, along with reductions in cardiovascular and respiratory illnesses, and mental health disorders. Greenspace may promote health, mitigate environmental pollution, and improve physical activity [16], which may reduce the risk of epilepsy. However, research on the effect of greenness on epilepsy remains uncertain. Considering the role of trees and vegetation in purifying air pollution and mitigating health effects, it is essential to investigate further how air pollutants may influence the linkage between greenness and epilepsy.

Notably, genetic susceptibility also acts critically in the development of epilepsy. Common variants explain 39.6% of genetic risk for genetic generalized epilepsy based on single-nucleotide polymorphism (SNP)-based heritability analyses [17]. In this regard, the polygenic risk score (PRS) was created using SNPs to identify individuals who may be at an elevated risk of developing epilepsy [18]. Examining how genetic susceptibility alters the relationship between environmental factors and epilepsy risk would help develop preventive strategies, especially in susceptible populations.

Considering these research gaps, we aimed to investigate the associations of exposure to residential greenness and air pollutants with the risk of incident epilepsy in 437,526 individuals from the UK Biobank. The novelty of this study lies in several key aspects: it is the first to examine the association of residential greenness and epilepsy risk; to quantify the modification effect of genetic susceptibility; to elucidate the potential mediating role of air pollution in the greenness-epilepsy association; and to evaluate the impact of environmental exposures on life expectancy among epileptics.

Methods

Study population

The data for our research were sourced from the UK Biobank, a substantial cohort involving over 500 thousand participants aged between 37 and 73 who were enrolled at the outset (2006–2010), as described previously [19]. Briefly, each subject completed touchscreen questionnaires and anthropometrics and agreed to provide biological specimens after signing an informed consent form. This cohort study received approval from the North West Multicenter Research Ethical Committee. Additional details regarding this cohort can be found at https://www.ukbiobank.ac.uk/.

The flowchart is presented in **Fig. S1**. From an initial pool of 502,479 individuals, we excluded 158 participants who withdrew consent. We further excluded 11,141 individuals with a history of brain injury, infection, benign and malignant tumors, and surgery at baseline (**Table S1**), 45,309 with missing environmental exposure data, and 8,345 with prevalent epilepsy. Prevalent epilepsy was also defined using antiepileptic drugs besides the first reported occurrence (**Table S2**), as applied in prior research [20]. Accordingly, a total of 437,526 subjects were included in the primary analysis. For the subsequent genetic analysis, 307,877 subjects of European descent were selected after removing missing data on SNPs and genotyping quality control. In addition, 8,345 individuals with prevalent epilepsy at/before baseline were assessed for life expectancy.

Assessment of outcomes

Incident epilepsy was identified by linkage to the "First occurrence" data (Field IDs: 131048–131051), including hospital inpatient and death records (ICD-9 and ICD-10), primary care data (Category 3000), and self-reported conditions (Field ID: 20002). Cases of epilepsy were determined using codes from both the ICD-9 and ICD-10 (ICD-9: 345; ICD-10: G40 and G41). All sources of data underwent verification. Participants were monitored from the point of recruitment until the diagnosis of epilepsy, loss to follow-up, death, or until the end of February 3, 2021, depending on which came first.

Residential greenness and air pollution

To assess residential greenness, the normalized difference vegetation index (NDVI) was calculated using data from a 16-day composite remote sensing product with a resolution of 250 m from the MODIS satellite after extracting the postcode for each subject residential address at recruitment [21,22]. The NDVI was derived based on the difference in chlorophyll absorption in the visible

red region (RED) (630–690 nm) and the reflection in the near-infrared region (NIR) (760–900 nm) of the electromagnetic spectrum, using the formula (NIR – RED)/(NIR + RED). The resulting values of NDVI can range from – 1 to 1. Typically, negative NDVI values indicate the presence of blue spaces or water, whereas higher values suggest the presence of denser green vegetation. All images underwent pre-processing to eliminate snowy pixels and clouds. NDVI values were constrained to be greater than 0 to avoid the impact of water bodies on health. To minimize seasonal variability and temporal mismatch, summer NDVI images (from July to August) were used to capture the baseline exposure of the UK Biobank (2006–2010). Given that different buffer sizes reflect distinct environmental exposures [23], we assessed NDVI within 300-, 500-, 1000-, and 1500-meter buffers around individual residences. A flowchart of the greenness exposure assessment is provided in **Fig. S2**.

The annual average concentrations of air pollutants, such as nitrogen oxide (NO_x), nitrogen dioxide (NO_2), particulate matter with a diameter of ≤ 2.5 μm ($PM_{2.5}$), and particulate matter with a diameter of ≤ 10 μm (PM_{10}), were analyzed utilizing land-use regression (LUR) [24,25]. This model, developed by the ESCAPE project, used GIS to assess personal exposure levels at the residential address. The assessment incorporated data on traffic volume, land use, topography, and population density. To evaluate the effectiveness of the LUR models, the leave-one-out cross-validation (LOOCV) technique was employed, yielding cross-validation R^2 values that varied between 77% and 88% [24,25]. In the UK Biobank, data on the annual average levels of PM10 and NO2 were accessible for multiple calendar years (specifically, PM10 for 2007 and 2010, NO2 for the years 2005, 2006, 2007, and 2010). Consequently, we calculated the mean estimates by averaging these values. In contrast, exposure data for $PM_{2.5}$ and NO_x were solely available for the year 2010.

Polygenic risk scores

Genetic data were assayed in the Affymetrix Research Services Laboratory, and its quality control was described at https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/ukb_dna_processing.pdf. We utilized 21 independent SNPs to calculate PRS that had a significance level of $P < 5 \times 10^{-8}$ and a minor allele frequency greater than 0.05, sourced from the largest Genome-Wide Association Study (GWAS) involving 29,944 individuals with epilepsy, of whom 92% were of European descent [17]. Detailed information is summarized in **Table S3**. Each SNP was assigned a value of 0, 1, or 2 based on the number of associated risk alleles. According to prior research [26], we computed the PRS using the formula: $PRS = \sum_i^{n=21} \beta \times \mathrm{SNP}$, where β was the coefficient of each variant for epilepsy. The PRS was categorized as low, medium, and high genetic risk based on the tertiles of the PRS among all participants. The subjects were classified into three categories of genetic risk—low, medium, and high—according to the tertiles of the PRS.

Covariates

Based on the directed acyclic graph (https://dagitty.net/) and prior literature [27,28], the models included potential confounders such as age, ethnicity, sex, body mass index (BMI), employment status, level of education, smoking habits, alcohol consumption, physical activity, and diet (**Fig. S3**). Physical activity was assessed using the Metabolic Equivalent Task (MET), calculated as the total minutes of activity per week according to the International Physical Activity Questionnaire. Additionally, the diet score was calculated using food frequency questionnaires including fish, processed meat, unprocessed red meat, fresh fruit, and vegetables, as described in **Table S4**. The higher the dietary score, the healthier the diet [29].

Statistical analysis

We conducted all statistical analyses using R 4.2.2, SAS 9.4, and Stata 16.0, considering a $P < 0.05$ threshold for statistical significance. Multiple testing was controlled by the false discovery rate (FDR) correction, with two-sided FDR-adjusted P-value < 0.05 considered statistically significant. Categorical variables were summarized using counts (percentages), while continuous variables that followed a normal distribution were expressed as means ± standard deviations (SD). The demographic characteristics were compared based on epilepsy status through the Chi-square and Student t-test. Missing covariates were filled in using missing indicators for categorical variables or employing median values for continuous variables. We also estimated the Pearson correlation coefficients of greenness and air pollutants.

To explore the relationship between greenness and air pollutants with the incidence of epilepsy, multivariate Cox models were applied. The models satisfied the proportional hazards hypothesis assessed by Schoenfeld residuals. This approach estimated hazard ratios (HRs) and 95% confidence intervals (CIs). The resulting HRs reflected the impacts of both residential greenness and air pollutants treated as continuous variables for each interquartile-range (IQR) change, as well as for categorized quartile variables. The assessment for linear trend was performed by treating each exposure group as a distinct integer values. The exposure–response curves were examined through restricted cubic spline (RCS) models incorporating three knots. Moreover, we assessed the joint effect of exposures on outcomes. And we also explored whether PRS may modify the relationship between greenness and air pollutants and epilepsy incidence. For genetic analyses, we further adjusted for the genotyping batch and the initial ten principal genetic components. To assess the multiplicative interactions, we incorporated cross-product terms into the models. Additive interactions were assessed with the synergy index (SI). An SI > 1 indicates synergy, where the combined effect exceeds the sum of individual effects, whereas an SI < 1 indicates antagonism, where one exposure attenuates the effect of the other [30]. The P-value for interaction less than 0.1 was considered suggestively significant. Assuming a causal association between exposure and outcome, the population-attributable risk (PAR%) was estimated using exposure prevalence and adjusted HRs of this category to quantify the proportion of epilepsy cases that could be prevented under low exposure [31].

Previous evidence suggested that air pollutants played an interactive or mediation role between greenness and diseases [32,33]. To evaluate the potential role of greenness and air pollutants, we used PROC CAUCALMED in SAS to perform causal mediation analyses [34,35]. This approach estimated air pollutants as potential mediators of greenness-epilepsy associations, allowing for interactions between greenness and air pollutants, with a P-value for the mediation of < 0.1 being considered suggestively significant. We decomposed the total greenness-epilepsy associations into four components to estimate the direct, mediating, and interactive effects in **Fig. S4.** Details of assumptions are provided in **Text S1**.

We also estimated the impact of residential greenness and air pollutants on life expectancy in epileptics using flexible parametric survival models with RCS to fit the baseline cumulative hazard (stpm2 command in Stata) [36]. This approach demonstrated superior performance compared to Cox models, particularly when assessing the life expectancy among smaller sizes [37]. Residual life expectancy was defined as the area under the survival curve up to age 100 to measure the potential time of survival for an individual or a population within a specific age range. Since the more

common and reliable mortality data for chronic diseases after 45 years, this study estimates life expectancy between 45 and 100 years [38]. The calculation of years of life gained was determined by the difference in area under the survival curve between healthier greenness or air pollution groups and the reference of unhealthy groups.

Some sensitivity analyses were performed to check the robustness of the results: 1) removing individuals with missing covariates; 2) using multiple imputation for missing covariates with the PROC MI and MIANALYZE MI and MIANALYZE in SAS; 3) excluding incident epilepsy cases that occurred within two years of follow-up to mitigate potential reverse causality; 4) limiting participants who have resided at the same address for more than five years; 5) employing Fine-Gray models to consider the death competition; 6) additionally adjusting for hypertension, diabetes, cardiovascular diseases (CVD), and cancer at baseline (**Table S5**); 7) additionally adjusting for noise pollution (Field ID: 24020–24024); 8) To minimize potential exposure misclassification from using baseline estimates, time-varying Cox models were applied to analyze exposure changes during the follow-up. Details of the time-varying exposure assessment are provided in **Text S2.** 9) including participants with brain injury, infection, benign and malignant tumors, and surgery at baseline; and additionally adjusted for these diseases. 10) After adjusting for measured confounders, the E-value was expressed as the minimum strength that unmeasured confounders would need to completely negate relationships between exposures and outcome [39].

Results

Baseline characteristics of study participants

During a median follow-up of 11.78 years, 2,448 incident epilepsy cases were identified among 437,526 participants. As shown in Table 1, individuals diagnosed with epilepsy tended to be older, predominantly male, with lower levels of education, and had higher prevalences of hypertension (66.4%), CVD (20.3%), diabetes (12.3%), and cancer (9.7%). Additionally, there were similar baseline characteristics across the dataset of the total population, main analysis, and genetic analysis. (**Table S6**). Residential greenness was negatively correlated with air pollutants, and the correlation coefficient ranged from –0.47 to –0.65 (**Fig. S5**).

Association of residential greenness and air pollutants with epilepsy incidence

After adjusting for covariates, each IQR increase in greenness (NDVI across all buffers) was associated with a 7–8% reduction in epilepsy risk. Conversely, each IQR increase in NO_2, NO_x, $PM_{2.5}$, and PM_{10} was associated with a 5–9% increased risk, with HRs (95% CIs) of 1.08 (1.03, 1.14), 1.05 (1.01, 1.09), 1.09 (1.04, 1.14), and 1.05 (1.00, 1.10), respectively (Fig. 1). The elevated quartiles of greenness and air pollutants were significantly associated with epilepsy risk (All $P_{trend} \leq 0.05$). Non-linear exposure–response relationship between NO_2 and epilepsy incidence ($P_{non\text{-}linear} = 0.036$) was found, while linear curves of greenness, NO_x, $PM_{2.5}$, and PM_{10} with epilepsy incidence ($P_{non\text{-}linear} > 0.05$, **Fig. S6**). The findings showed stability across all sensitivity analyses (**Table S7** and **Table S8**). Of note, in a sensitivity analysis based on time-varying exposure estimates, the HRs (95% CIs) for each IQR increase were as follows: 0.90 (0.89, 0.92), 0.90 (0.89, 0.92), 0.88 (0.86, 0.89), and 0.87 (0.85, 0.88), for $NDVI_{300m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{1500m}$, respectively; and 1.05 (1.03, 1.07), 1.03 (1.01, 1.04), 1.17 (1.16, 1.19), and 1.21 (1.19, 1.23) for NO_2, NO_x, $PM_{2.5}$, and PM_{10}. E-values in our study were greater than the HRs (**Table S9**), meaning that unmeasured confounders were unlikely to offset these associations. The PAR% associated with greenness and air pollutants ranged from 16.1% (1.9%, 29.7%) to 24.3% (11.0%, 36.7%) (**Table S10**). In brief, higher greenness was associated with a reduced risk of epilepsy, whereas increased air pollution exposure was linked to an elevated risk.

Causal mediation effects of air pollutants

In causal mediation analysis, $PM_{2.5}$ was suggested to mediate 38.26% (–4.01%, 80.53%), 48.38% (–4.58%, 101.35%), 47.73% (–4.65%, 100.11%), 39.59% (–3.89%, 83.07%) of the associations of $NDVI_{300m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{1500m}$ with epilepsy incidence, respectively (Table 2**,** all $P_{mediation} < 0.1$). The proportions attributable to antagonistic interactions between residential greenness and $PM_{2.5}$ accounted for 0.88%-0.93%. We also observed the antagonistic interaction effects for $NDVI_{300m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{1500m}$ with NO_2 accounted for –0.88% (–1.44%, –0.32%), –0.89% (–1.36%, –0.42%), –0.91% (–1.40%, –0.42%), –0.92% (–1.50%, –0.35%) of the overall association for greenness and epilepsy risk. In summary, the reduction in the risk of epilepsy caused by residential greenness was partially mediated by lower levels of $PM_{2.5}$.

Modification effects of genetic susceptibility

For each unit increase in PRS as a continuous variable, the risk of incident epilepsy increased by 68% [1.68 (1.30, 2.15), **Table S11**]. Participants with high PRS had 30% increased epilepsy risk [1.30 (1.15, 1.46), $P_{trend} < 0.001$] compared with those with the lowest PRS. Moreover, we investigated the combined influence of greenness, air pollutants, and PRS on epilepsy risk (Fig. 2). When comparing individuals with high greenness and low PRS exposure, those with low greenness exposure and high PRS had higher epilepsy risk [$NDVI_{300m}$: 1.59 (1.24, 2.04); $NDVI_{500m}$: 1.48 (1.16, 1.90); $NDVI_{1000m}$: 1.49 (1.16, 1.90); $NDVI_{1500m}$: 1.47 (1.15, 1.87)]. Similarly, subjects who were exposed to both high levels of PRS and air pollutants demonstrated a greater risk of epilepsy than those with both low levels of PRS and air pollutants [NO_2: 1.62 (1.27, 2.07); NO_X: 1.62 (1.26, 2.08); $PM_{2.5}$: 1.69 (1.31, 2.17); PM_{10}: 1.38 (1.08, 1.77)]. There were antagonistic additive [all SIs (95% CIs) < 1] and multiplicative interactions (all $P_{interaction} < 0.1$) between greenness and PRS, but not for air pollutants (Table 3). Specifically, the antagonistic effect signified that high greenness partially offset the increased epilepsy risk conferred by genetic susceptibility. In a word, genetic susceptibility significantly modified the relationship between greenness and epilepsy.

Life expectancy in patients with epilepsy

At age 45 years, life expectancy was 36.89 (36.21, 37.56) years for epileptics and 41.39 (40.85, 41.93) years for individuals without epilepsy, indicating that epileptics lived 4.50 years less (**Fig. S7**). Among epileptics, individuals with the highest quartile of $NDVI_{300m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{1500m}$ gained life years of 2.15 (0.68, 3.62), 2.67 (1.12, 4.22), 2.24 (0.75, 3.74), and 2.23 (0.72, 3.74) at age 45 years, respectively, compared to those with the lowest greenness exposures (Fig. 3). At age 45 years, the life expectancy of epileptics in the lowest quartile of air pollutants increased by 1.76 to 2.51 years compared to those in the highest exposures. The findings highlighted that higher residential greenness and lower air pollutants were linked to significantly longer life expectancy in epileptics.

Table 1
Baseline characteristics of participants by incident epilepsy during follow-up.

Characteristics	Overall (*n* = 437526)	Non-epilepsy (*n* = 435078)	Incident epilepsy (*n* = 2448)	*P*-value
Age at recruitment (years)	56.58 ± 8.09	56.57 ± 8.09	58.97 ± 7.89	<0.001
Sex (Male, %)	198,782 (45.4)	197,497 (45.4)	1285 (52.5)	<0.001
Body mass index (BMI, kg/m^2)	27.41 ± 4.78	27.41 ± 4.78	27.91 ± 5.08	<0.001
Missing	2492 (0.6)	2464 (0.6)	28 (1.1)	
Ethnicity (White, %)	410,364 (93.8)	408,056 (93.8)	2308 (94.3)	0.060
Missing	2422 (0.6)	2402 (0.6)	20 (0.8)	
Education level, n (%)				<0.001
College or University degree	138,236 (31.6)	137,650 (31.6)	586 (23.9)	
Non-college or other professional	217,371 (49.7)	216,208 (49.7)	1163 (47.5)	
None of the above	72,783 (16.6)	72,153 (16.6)	630 (25.7)	
Missing	9136 (2.1)	9067 (2.1)	69 (2.8)	
Employment status, n (%)				<0.001
Employed	251,764 (57.5)	250,781 (57.6)	983 (40.2)	
Retired	146,016 (33.4)	144,934 (33.3)	1082 (44.2)	
Unemployed, home maker, or other	37,147 (8.5)	36,785 (8.5)	362 (14.8)	
Missing	2599 (0.6)	2578 (0.6)	21 (0.9)	
Drinking status, n (%)				<0.001
Never	19,296 (4.4)	19,163 (4.4)	133 (5.4)	
Previous	14,727 (3.4)	14,577 (3.4)	150 (6.1)	
Current	402,105 (91.9)	399,959 (91.9)	2146 (87.7)	
Missing	1398 (0.3)	1379 (0.3)	19 (0.8)	
Smoking status, n (%)				<0.001
Never	239,095 (54.6)	237,961 (54.7)	1134 (46.3)	
Previous	151,513 (34.6)	150,584 (34.6)	929 (37.9)	
Current	44,384 (10.1)	44,020 (10.1)	364 (14.9)	
Missing	2534 (0.6)	2513 (0.6)	21 (0.9)	
Physical activity (MET)				<0.001
≤Median	174,608 (39.9)	173,650 (39.9)	958 (39.1)	
>Median	175,773 (40.2)	174,859 (40.2)	914 (37.3)	
Missing	87,145 (19.9)	86,569 (19.9)	576 (23.5)	
Healthy diet score, n (%)				<0.001
0–1	96,020 (21.9)	95,445 (21.9)	575 (23.5)	
2–3	274,920 (62.8)	273,466 (62.9)	1454 (59.4)	
4–5	56,961 (13.0)	56,635 (13.0)	326 (13.3)	
Missing	9625 (2.2)	9532 (2.2)	93 (3.8)	
Hypertension, n (%)	239,824 (54.8)	238,199 (54.7)	1625 (66.4)	<0.001
Diabetes, n (%)	26,941 (6.2)	26,640 (6.1)	301 (12.3)	<0.001
Cardiovascular diseases, n (%)	40,360 (9.2)	39,864 (9.2)	496 (20.3)	<0.001
Cancer, n (%)	35,977 (8.2)	35,740 (8.2)	237 (9.7)	0.009
$NDVI_{300m}$	0.57 ± 0.11	0.57 ± 0.11	0.56 ± 0.11	<0.001
$NDVI_{500m}$	0.57 ± 0.10	0.57 ± 0.10	0.56 ± 0.10	<0.001
$NDVI_{1000m}$	0.58 ± 0.10	0.58 ± 0.10	0.57 ± 0.09	<0.001
$NDVI_{1500m}$	0.58 ± 0.09	0.58 ± 0.09	0.57 ± 0.09	<0.001
NO_2 (μg/m^3)	29.27 ± 9.21	29.27 ± 9.21	29.85 ± 8.93	0.002
NO_x (μg/m^3)	43.97 ± 15.59	43.96 ± 15.59	45.02 ± 15.56	0.001
$PM_{2.5}$ (μg/m^3)	9.99 ± 1.05	9.99 ± 1.05	10.09 ± 1.10	<0.001
PM_{10} (μg/m^3)	19.31 ± 1.94	19.31 ± 1.94	19.37 ± 1.87	0.118

Mean values (standard deviation) for normal continuous variables and n (%) for categorical variables.

Discussion

As far as we are aware, this research is the first investigation into the association between residential greenness and epilepsy risk. Our research showed that prolonged exposures to greenness and air pollutants were notably linked to the risk of incident epilepsy in the large-scale prospective cohort. We observed significant interactions of gene-greenness. Furthermore, we not only found significant antagonistic effects between NO_2, $PM_{2.5}$, and residential greenness on epilepsy incidence but also observed that $PM_{2.5}$ mediated the relationship of greenness with epilepsy. Notably, epileptics with high greenness or low air pollution had an increased life expectancy of 1.76 to 2.67 years at age 45 years, compared with epileptics with low greenness or high air pollution.

So far, there have been a few human studies examining the relationships between exposure to air pollutants and the incidence of epilepsy. For instance, time-series analyses showed that short-term exposure to carbon monoxide (CO), ozone (O_3), sulfur dioxide (SO_2), NO_2, $PM_{2.5}$, and PM_{10} were associated with hospitalization for epilepsy in Chile [7], but not in the United States [40]. Also, correlations were found between NO_2 and SO_2 with increased outpatient visits for epilepsy, whereas O_3 demonstrated a relationship with a decreased risk [8]. Previous research has mainly addressed the acute effects of air pollution with mixed results, whereas evidence on long-term exposure and epilepsy risk is scarce. A nested case–control study observed a higher risk of new-onset epilepsy in relation to $PM_{2.5}$ and O_3 exposure [15]. In this study, long-term exposure to NO_2, NO_x, $PM_{2.5}$, and PM_{10} was linked to a heightened risk of epilepsy. The PAR% for air pollutants ranged from 16.1% to 20.8%. If the observed associations are causal, this would indicate that 16.1–20.8% of incident epilepsy cases could potentially be prevented through air quality improvement. This estimate must be interpreted with caution, given the observational nature of our study.

There are several key pathways through which air pollutants can lead to the occurrence of epilepsy. Established mechanisms included the entry of PM and gaseous pollutants into the brain via the bloodstream or olfactory nerve, leading to neuroinflammation—mediated by astrocytic and microglial activation and cytokine release—and oxidative stress through the

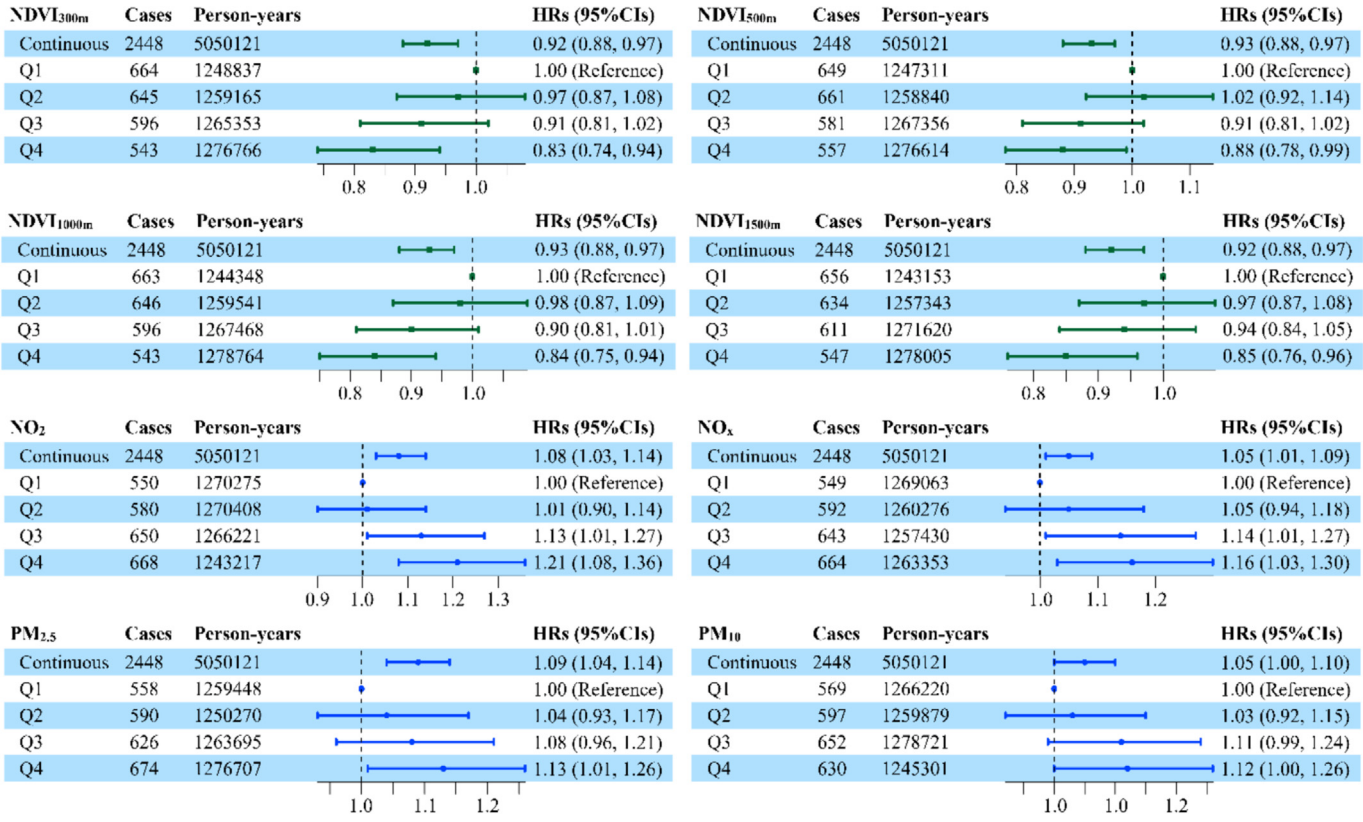

Fig. 1. Adjusted HRs (95% CIs) of the risk of incident epilepsy by residential greenness and air pollution. Model was adjusted for age at recruitment, BMI, sex, ethnicity, education level, employment status, smoking status, drinking status, MET, and healthy diet score. Continuous represented HRs changes in residential greenness and air pollution for per increase interquartile range. The *P* values for trend were 0.001, 0.007, 0.001, 0.006, <0.001, 0.005, 0.032, and 0.022 for $NDVI_{300m}$, $NDVI_{500m}$, $NDVI_{1000m}$, $NDVI_{1500m}$, NO_2, NO_x, $PM_{2.5}$, and PM_{10}, respectively. Abbreviations: HRs, hazard ratios; CIs, confidence intervals; Q, quantile; $NDVI_{300m}$, normalized difference vegetation index within 300 m buffer; $NDVI_{500m}$, normalized difference vegetation index within 500 m buffer; $NDVI_{1000m}$, normalized difference vegetation index within 1000 m buffer; $NDVI_{1500m}$, normalized difference vegetation index within 1500 m buffer, $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Table 2
Proportions attributable to interaction and mediation of the associations between incident epilepsy and residential greenness mediated and interacted by air pollution.

Exposure	NO_2		NO_x		$PM_{2.5}$		PM_{10}	
	Mediation (%)	Interaction (%)	Mediation (%)	Interaction (%)	Mediation (%)	Interaction (%)	Mediation (%)	Interaction (%)
$NDVI_{300m}$	31.12 (−11.31, 73.55)	**−0.88 (−1.44, −0.32)**	13.87 (−14.80, 42.55)	−0.50 (−1.28, 0.28)	38.26 (−4.01, 80.53)*	**−0.93 (−1.36, −0.51)**	2.95 (−31.95, 37.86)	−0.13 (−1.55, 1.30)
$NDVI_{500m}$	41.06 (−12.69, 94.82)	**−0.89 (−1.36, −0.42)**	18.02 (−16.35, 52.38)	−0.56 (−1.28, 0.17)	48.38 (−4.58, 101.35)*	**−0.88 (−1.45, −0.32)**	5.71 (−36.11, 47.54)	−0.21 (−1.65, 1.22)
$NDVI_{1000m}$	42.46 (−15.47, 100.40)	**−0.91 (−1.40, −0.42)**	17.76 (−17.03, 52.54)	−0.56 (−1.31, 0.20)	47.73 (−4.65, 100.11)*	**−0.89 (−1.44, −0.34)**	−3.49 (−41.18, 48.16)	−0.13 (−1.78, 1.51)
$NDVI_{1500m}$	35.00 (−17.07, 87.08)	**−0.92 (−1.50, −0.35)**	14.56 (−16.30, 45.42)	−0.51 (−1.33, 0.30)	39.59 (−3.89, 83.07)*	**−0.92 (−1.35, −0.50)**	−0.86 (−42.82, 41.09)	0.04 (−1.82, 1.89)

Causal mediation models include adjustment for age at recruitment, sex, ethnicity, BMI, education level, employment status, smoking status, drinking status, MET, and healthy diet score. Abbreviations: CIs, confidence intervals; $NDVI_{300m}$, normalized difference vegetation index within 300 m buffer; $NDVI_{500m}$, normalized difference vegetation index within 500 m buffer; $NDVI_{1000m}$, normalized difference vegetation index within 1000 m buffer; $NDVI_{1500m}$, normalized difference vegetation index within 1500 m buffer, $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides. * *P*-value < 0.1 is suggested statistical significance. Bold text indicates *P*-value < 0.05.

production of reactive oxygen and nitrogen species (ROS/RNS) [6,41]. Experimental evidence further showed that these inflammatory and oxidative responses can trigger neuronal hyperexcitability, thereby increasing seizure susceptibility [42]. A recent study in both epileptic patients and mice also found that high $PM_{2.5}$ exposure may exacerbate seizure symptoms and cognitive dysfunction by disrupting iron metabolism and the Nrf2-mediated ferroptosis pathway [43]. Thus, further studies are required to fully clarify the causal relevance of these mechanisms in human epilepsy.

The negative association observed between residential greenness and epilepsy incidence can be interpreted through several mechanistic pathways. An established pathway, trees and plants absorbed gaseous pollutants (e.g., NO_x, SO_2, O_3) via leaf stomata and intercepted PM on their surfaces [44,45]. In line with this, we also found suggestive evidence that $PM_{2.5}$ mediated 38.26% to 48.38% of the association between greenness and epilepsy incidence. The wide confidence intervals, which included the null, indicate statistical instability, thus, these mediation estimates should be interpreted with caution and require further validation.

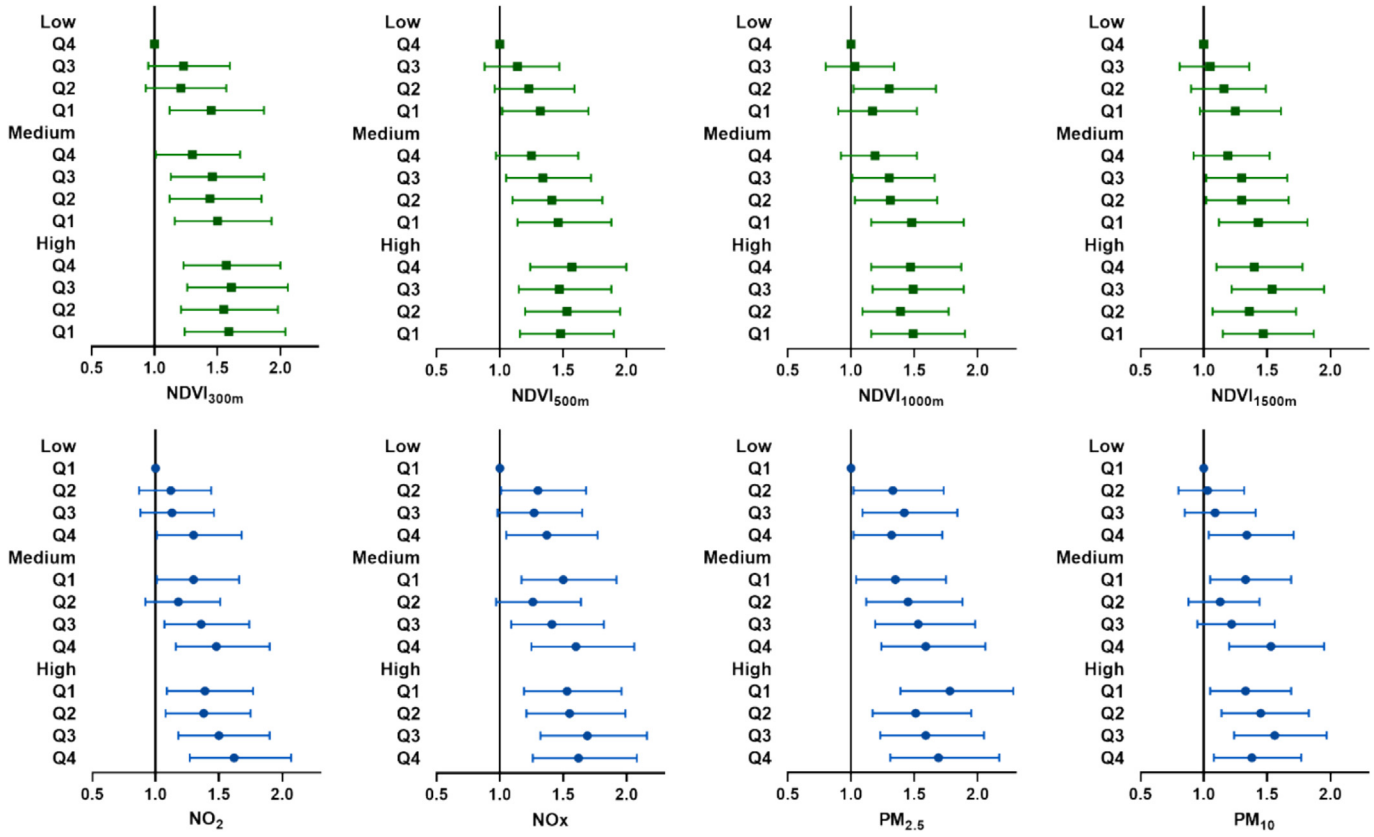

Fig. 2. Joint effects of the residential greenness and air pollution exposure and PRS on the risk of incident epilepsy. Model was adjusted for age at recruitment, BMI, sex, education level, employment status, smoking status, drinking status, MET, healthy diet score, genotyping batch, and the first ten genetic principal components. Abbreviations: HRs, hazard ratios; CIs, confidence intervals; PRS, polygenic risk score; $NDVI_{300m}$, normalized difference vegetation index within 300 m buffer; $NDVI_{500m}$, normalized difference vegetation index within 500 m buffer; $NDVI_{1000m}$, normalized difference vegetation index within 1000 m buffer; $NDVI_{1500m}$, normalized difference vegetation index within 1500 m buffer, $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Table 3
Interaction between environmental exposures and genetic susceptibility on the epilepsy incidence.

Interaction	Residential greenness				Air pollution			
	$NDVI_{300m}$	$NDVI_{500m}$	$NDVI_{1000m}$	$NDVI_{1500m}$	NO_2	NO_x	$PM_{2.5}$	PM_{10}
Additive interaction								
SI (95% CI)	0.656 (0.596, 0.722)	0.661 (0.598, 0.732)	0.663 (0.592, 0.742)	0.679 (0.608, 0.759)	1.035 (0.969, 1.105)	1.028 (0.884, 1.195)	1.158 (0.948, 1.414)	1.122 (0.910, 1.384)
P for additive interaction	**0.020**	**0.023**	**0.016**	**0.066**	0.407	0.626	0.626	0.686
Multiplicative interaction								
P for multiplicative interaction	**0.022**	**0.026**	**0.023**	**0.061**	0.580	0.846	0.189	0.296

Model was adjusted for age at recruitment, BMI, sex, education level, employment status, smoking status, drinking status, MET, healthy diet score, genotyping batch, and the first ten genetic principal components. Abbreviations: SI, synergy index; CIs, confidence intervals; $NDVI_{300m}$, normalized difference vegetation index within 300 m buffer; $NDVI_{500m}$, normalized difference vegetation index within 500 m buffer; $NDVI_{1000m}$, normalized difference vegetation index within 1000 m buffer; $NDVI_{1500m}$, normalized difference vegetation index within 1500 m buffer, $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

Moreover, the proportions attributable to antagonistic interactions between greenness, NO_2, and $PM_{2.5}$ accounted for 0.88%-0.93%. This observation aligned with a recent study of minor interaction effect concerning greenness and $PM_{2.5}$ in relation to mortality [33]. Other potential pathways include increased physical activity and reduced psychological stress associated with greenspace exposure, which may indirectly support neurological health [16]. However, the specific role of these mechanisms in epilepsy prevention remains hypothetical and warrants confirmation in future studies.

Strong evidence indicated that genetic predisposition was crucial in the onset of epilepsy [17]. Additionally, combined effects revealed that elevated exposure to high air pollutants or low levels of greenness, along with high genetic risk, heightened the risk of developing epilepsy. Significant antagonistic interactions between greenness and PRS were also observed. This finding suggested that it was a priority for individuals with high genetic risk to increase residential greenness. Our study also showed that epileptics had a life expectancy of 4.50 years shorter at age 45 years than those

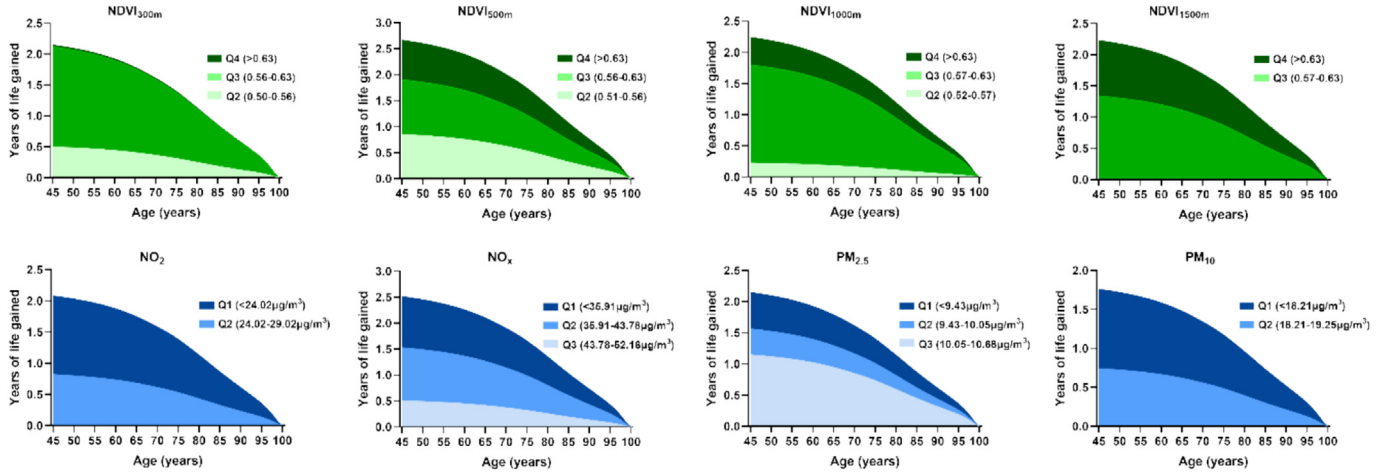

Fig. 3. Life year gains associated with residential greenness and air pollution when compared to the lowest greenness or highest air pollution group for epileptics. Model was adjusted for age at recruitment, sex, ethnicity, BMI, education level, employment status, smoking status, drinking status, MET, and healthy diet score. Abbreviations: Q, quantile; $NDVI_{300m}$, normalized difference vegetation index within 300 m buffer; $NDVI_{500m}$, normalized difference vegetation index within 500 m buffer; $NDVI_{1000m}$, normalized difference vegetation index within 1000 m buffer; $NDVI_{1500m}$, normalized difference vegetation index within 1500 m buffer, $PM_{2.5}$, fine particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides.

without epilepsy. A prior study indicated that individuals with epilepsy faced a threefold increased risk of early mortality when compared to the general population [46]. To provide comprehensive care and treatment for epileptics, the World Health Organization released a bulletin entitled "Improving the lives of people with Epilepsy" in 2022. Notably, our findings indicated that epileptics with high greenness or low air pollution had an increased life expectancy of 1.76 to 2.67 years at age 45 years, compared with epileptics with low greenness or high air pollution. Therefore, enhancing urban greenness and reducing air pollution may prevent epilepsy and improve long-term outcomes.

This study's strengths comprised a substantial sample size, the assessment of both relative and absolute risks of epilepsy, the examination of gene-environment interactions, and further exploration underlying role of air pollution. Additionally, reliable nationwide data were used to calculate life expectancy. However, several potential limitations have been noted in our study. First, we only estimated the overall greenness coverage via NDVI but did not obtain information on specific types of vegetation. Second, several studies reported that CO, O_3, and SO_2 were related to the risk of epilepsy, but these were not available in our study. Third, our exposure assessment did not obtain relevant information on workplaces and individual activity patterns, yielding a potential for non-differential misclassification that would typically bias results towards the null [47]. Future studies should use portable and automated monitoring to improve individual exposure assessment of air pollution and greenness. Fourth, the completeness of epilepsy ascertainment warrants consideration. In the UK, there was a high positive predictive value (93–98%) but lower sensitivity (83–88%) due to limited outpatient and primary care data [48,49]. Our use of "First occurrence" data, incorporating primary care and self-reported diagnoses, likely reduced this limitation. Any residual misclassification would be non-differential and thus bias estimates toward the null, but significant associations in this study were still observed. Additionally, epilepsy subtypes were not examined, highlighting the need for future research on specific epilepsy types. Fifth, our PRS derived using the clumping and thresholding method captured the major common genetic susceptibility from the strongest risk variants, but did not represent the full polygenic architecture of epilepsy. Future studies employing more comprehensive PRS are warranted to better elucidate gene-environment interactions. Sixth, although some covariates were controlled for, there remains a possibility that unmeasured and residual confounders, which may have influenced our analyses. Finally, the generalizability of our findings was limited, as the UK Biobank represents a predominantly White, high-income population. Environmental exposures, healthcare access, and urban infrastructure vary across countries with different income levels, partly reflecting differences in epilepsy burden [50]. Therefore, further studies in populations with diverse geographic, socioeconomic, and ethnic backgrounds are needed to validate these findings.

Conclusion

In this large-scale prospective cohort, residential greenness and air pollutants were significantly associated with both epilepsy incidence and life expectancy. These associations between residential greenness and epilepsy were modified by genetic susceptibility and partially mediated by air pollution. Although these findings highlight the potential of environmental interventions, they remain observational and require validation in independent, diverse populations and via quasi-experimental studies to strengthen causal inference.

Ethics approval and consent to participate

The ethics approval was authorized by the North West Multicenter Research Ethics Committee (reference no. 16/NW/0274). All participants provided informed consent to participate.

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.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2026.01.043.

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