Extended method section

Data collection

To assess the correlation between RA and brain, we conducted an analysis using neuropsychiatric disorders and neuroimaging data obtained from the UKB cohort which contains 502411 participants. The RA diagnose was according to previous study [1]. The basic covariant in our study includes age, sex, education attainment and blood pressure. The participants without information about these basic covariant are excluded from the cohort. Educational attainment was categorized into two groups: individuals with a college degree and those without. Hypertension was defined based on measured blood pressure values, with individuals having a systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg being classified as hypertensive. Moreover, the participants with other kinds of arthritis like osteoarthritis, gout, PsA and infectious arthritis or without follow-up information were excluded from the cohort. To further evaluate the effect of estrogen on neuropsychiatric diseases, we also collect data about if had menopause and ever used hormone-replacement therapy (HRT). At last, totally 27485 participants were chosen for further correlation analysis. The detailed characteristic information was showed in **Supplementary table 1** and the information about the field ID of the basic covariant was presented in **Supplementary table 2.**

Neuropsychiatric disorders

Neuropsychiatric disorders include all-cause dementia, delirium, schizophrenia, depressive episode, adjustment disorders, and personality disorders. The information about the field ID of the neuropsychiatric disorders was presented in **Supplementary table 2**. 855 participants lost the information about neuropsychiatric disorders were excluded. Finally, totally 26630 participants were included. To assess the association between RA and neuropsychiatric disorders, logistic regression models were performed: (1) Model 1: Without any adjustments. (2) Model 2: Adjusting for age and gender (both sex). (3) Model 3: Adjusting for education and blood pressure based on Model 2. The estimate of logistic regression model represented the odds ratio for

diseases. More detailed method information was included in supplementary information. Moreover, seventy-five patients with clear RA onset time and other covariate information were used to assess the correlation between the number of days after RA diagnosis and brain volume, neuropsychiatric diseases, and the RCS curve was utilized to demonstrate the regression model of the correlation.

Brain structure

To account for potential confounding factors related to neurocognition, individuals with rheumatoid arthritis (RA) and healthy controls (HC) were meticulously matched in a 1:2 ratio based on age, sex, education, and hypertension status. Using structural MRI data from the UK Biobank dataset (the information about the field ID of the structural MRI data was presented in **Supplementary table 2**), we examined the impact of RA on atrophy of gray matter volume in 139 anatomical regions, measured in mm^3 (RA: N = 217; HC: N = 434, **Supplementary fig 1**). To assess the extent of atrophy in each anatomical region relative to the mean gray matter volume, we employed linear regression. The estimated regression coefficients and their 95% confidence intervals were divided by the average gray matter volume. This allowed us to quantify the atrophy in each region as a relative percentage change from the mean gray matter volume.

Brain activity

To further assess the effect of RA on brain activity, resting-state functional magnetic resonance imaging (rs-fMRI) data from the UKB dataset (the information about the field ID of the structural MRI data was presented in **Supplementary table 2**) were analyzed after a 1: 2 ratios participants match (RA: N = 184; HC: N = 368, **Supplementary fig 2**). The raw data have been pre-processed by UKB according to their standard pipeline[2].And then we utilized DPASFA Software （http://rfmri.org/DPARSF）, DPABI Software (http://rfmri.org/DPABI), and SPM12 Software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), all based on the MATLAB platform (Math Works; http://www.mathworks.com/products/matlab/), for advanced data processing. To ensure data quality and minimize confounding factors, several preprocessing steps were performed on the rs-fMRI data. Firstly, the

initial 10 volumes of each functional time series were discarded to account for scanner calibration and allow participants to adapt to the scanning environment. Slice time correction and head motion correction were then applied to address potential artifacts. Subjects with excessive head motion exceeding 2 mm or head rotation greater than 2° in any direction were excluded from further analysis. Furthermore, the average framewise displacement (FD) was computed for each subject to quantify motion-related artifacts. Time points with FD values exceeding 0.5 mm were removed to mitigate the impact of motion artifacts on the data. It is important to note that all subjects included in the study met the criteria for exercise participation, and no participants were excluded from the final analysis based on these criteria. To establish spatial correspondence between functional and structural images, the rs-fMRI data were registered to their corresponding high-resolution T1-weighted anatomical images. This registration process ensured accurate alignment between the two modalities. Subsequently, the fMRI images were normalized to the standardized Montreal Neurological Institute (MNI) template, enabling comparison and integration across different individuals and studies. The resulting images were resampled to a voxel size of 3 mm × 3 mm × 3 mm to achieve consistent spatial resolution. To improve the signal-to-noise ratio and facilitate statistical analysis, we applied spatial smoothing to the normalized fMRI images using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm.

Brain activation was quantified by calculating the amplitude of low-frequency fluctuation (ALFF) within the frequency range of 0.01 - 0.08 Hz. To enhance normality and ensure comparability between subjects, ALFF values for each voxel were normalized using Z-score transformation, accounting for differences in absolute signal intensity. The resulting z-scored ALFF (zALFF) images were subjected to statistical analysis using spm12. Group differences in zALFF variability between individuals with RA and healthy controls (HC) within the entire population were evaluated using a two-sample t-test, with age, sex, education level, hypertension, and FD serving as covariates. To control for multiple comparisons, cluster-level family-wise error (FWEc) correction was applied. The voxel-level statistical threshold

was set at $P < 0.001$, the cluster-level threshold was set at $P < 0.05$, and only brain regions consisting of clusters with a minimum size of 30 voxels were considered as significant difference brain regions. The same method was used to compare the differences of zALFF between RA and HC of the same sex (RA_{male}: N = 57; HC_{male}: N = 114; RA_{female}: N = 127; HC_{female}: N = 254, **Supplementary fig 2**).

Analysis and software

Analyses, including linear and logistic regression, were executed utilizing R (version 4.2.2). For the visualization of the data, the R package 'ggplot2' was employed.

Reference

1. Harnden, K., Pease, C. & Jackson, A. Rheumatoid arthritis. *BMJ* **352**, i387 (2016).

Supplementary tables

Supplementary table 1.

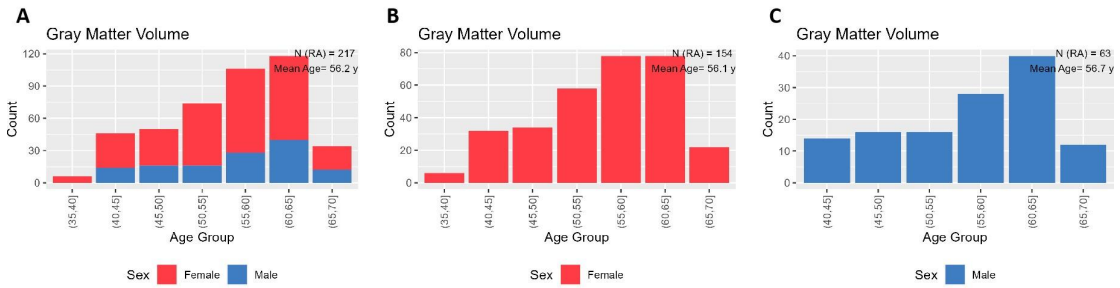
Characteristics of the cohort			
	HC (N=27200)	**RA (N=285)**	**Total (N=27485)**
sex			
Female	13881 (51.0%)	199 (69.8%)	14080 (51.2%)
Male	13319 (49.0%)	86 (30.2%)	13405 (48.8%)
age			
Mean (SD)	54.1 (7.62)	56.3 (7.44)	54.1 (7.62)
Median [Min, Max]	54.0 [40.0, 70.0]	57.0 [40.0, 70.0]	54.0 [40.0, 70.0]
bp			
NBP	13846 (50.9%)	133 (46.7%)	13979 (50.9%)
HBP	13354 (49.1%)	152 (53.3%)	13506 (49.1%)
edu			
NCD	12899 (47.4%)	156 (54.7%)	13055 (47.5%)
CD	14301 (52.6%)	129 (45.3%)	14430 (52.5%)

Abbreviation: blood pressure (bp), normal blood pressure (NBP), high blood pressure (HBP), education (edu), do not possess college degree (NCD), possess college degree (CD).

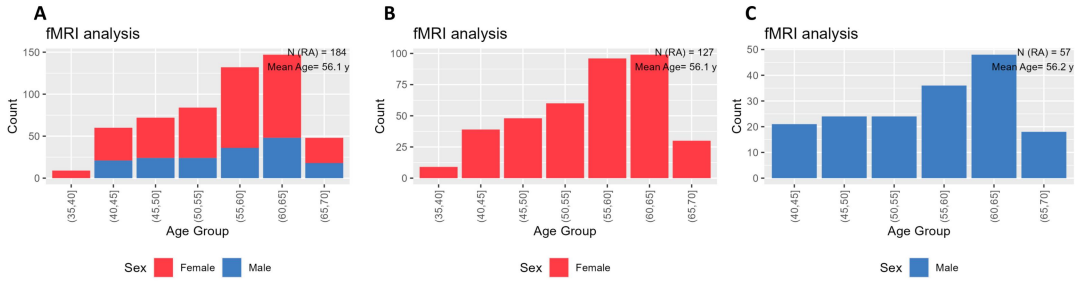
Supplementary table 2.

Field ID in UKbiobank		
Description	**Field ID**	**Category**
Sex	31	Baseline characteristics
Age	21003	Reception
Systolic blood pressure	4080	Blood pressure
Diastolic blood pressure	4079	Blood pressure
Qualifications	6138	Education
All-cause dementia	42018	Dementia outcomes
Delirium	130846	Mental and behavioural disorders
Schizophrenia	130874	Mental and behavioural disorders
Depressive episode	130894	Mental and behavioural disorders
Adjustment disorders	130910	Mental and behavioural disorders
Personality disorders	130932	Mental and behavioural disorders
Volume of grey matter	25782-25920	Regional grey matter volumes (FAST)
fMRI images	20227	Resting functional brain MRI
Had menopause	2724	Female-specific factors
Ever used hormone-replacement therapy	2814	Female-specific factors

Supplementary figures



Supplementary fig 1. Sample size distributions of the analysis of the gray matter volume.



Supplementary fig 2. Sample size distributions of the fMRI analysis.